

Reassessing Patterns of Response to Immunotherapy with PET: From Morphology to Metabolism

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Abbreviations: CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, EORTC = European Organization for Research and Treatment of Cancer, FDG = fluorodeoxyglucose, ICI = immune checkpoint inhibitor, irAE = immune-related adverse event, iRECIST = modified RECIST 1.1 for immune-based therapeutics, MIP = maximum intensity projection, PD-L1 = programmed cell death ligand 1, PD-1 = programmed cell death protein 1, PERCIST = PET Response Criteria in Solid Tumors, RECIST = Response Evaluation Criteria in Solid Tumors, SUV = standardized uptake value

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Cancer demands precise evaluation and accurate and timely assessment of response to treatment. Imaging must be performed early during therapy to allow adjustments to the course of treatment. For decades, cross-sectional imaging provided these answers, showing responses to the treatment through changes in tumor size. However, with the emergence of immune checkpoint inhibitors, complex immune response patterns were revealed that have quickly highlighted the limitations of this approach. Patterns of response beyond tumor size have been recognized and include cystic degeneration, necrosis, hemorrhage, and cavitation. Furthermore, new unique patterns of response have surfaced, like pseudoprogression and hyperprogression, while other patterns were shown to be deceptive, such as unconfirmed progressive disease. This evolution led to new therapeutic evaluation criteria adapted specifically for immunotherapy. Moreover, inflammatory adverse effects of the immune checkpoint blockade were identified, many of which were life threatening and requiring prompt intervention. Given complex concepts like tumor microenvironment and novel therapeutic modalities in the era of personalized medicine, increasingly sophisticated imaging techniques are required to address the intricate patterns of behavior of different neoplasms. Fluorine 18–fluorodeoxyglucose PET/CT has rapidly emerged as one such technique that spans both molecular biology and immunology. This imaging technique is potentially capable of identifying and tracking prognostic biomarkers owing to its combined use of anatomic and metabolic imaging, which enables it to characterize biologic processes in vivo. This tailored approach may provide whole-body quantification of the metabolic burden of disease, providing enhanced prediction of treatment response and improved detection of adverse events.

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Discuss the role of metabolic tumor assessment with ¹⁸F-FDG PET/CT and review the status of the currently available response assessment criteria—anatomic and metabolic.
- Recognize the usual and unusual patterns of response to immunotherapy.
- Identify typical adverse events associated with immunotherapy.

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Introduction

Avoidance of the host immune response is a recognizable hallmark of cancer (1). Several approaches based on the induced immune response against tumors (ie, cancer immunotherapy) have been tested in past decades, including exogenous antigens, vaccines, and immune system modulators (2). However, in the past few years, the emergence of

TEACHING POINTS

- PET—particularly fluorodeoxyglucose (FDG) PET—can provide valuable discriminative power regarding oncologic response and also aid in prognostication and early detection of irAEs. As a metabolism-based imaging technique, FDG PET allows detection of tumor activity or viability or irAEs with higher sensitivity and can show early tumor functional changes in response to therapy.
- Regardless of the adopted imaging criteria, the most important information in oncologic assessment of therapeutic response is definition of one of the four possible patterns: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), with some possible adaptation according to the antineoplastic agent used.
- There is a strong relationship between FDG uptake and the number of viable cancer cells. A reduction in FDG uptake usually denotes treatment response, which precedes changes in tumor size. Therefore, PET/CT may be used for assessing response to immunotherapy early after initiating treatment to predict efficacy, at midtreatment, and at the end of treatment. Analysis of FDG PET results combines subjective visual analysis and objective semiquantitative measurement of SUV_{max} .
- The most important change in immune-related response criteria (such as iRECIST) is implementation of different time points for assessing early progressive disease.
- After the start of ICI therapy, irAEs commonly manifest within the first 3 months of administration for most drugs. Moreover, there is also a tendency for a temporal pattern of toxic effects to manifest after commencement of therapy: dermatologic effects are noted first (within 2–3 weeks), followed by gastrointestinal or hepatic effects (within 6–7 weeks), pulmonary effects (within 9 weeks), and endocrine-related effects (within 9–11 weeks). With anti-CTLA-4 drugs, such manifestations tend to occur somewhat earlier than with other ICIs. Despite such a pattern, any irAE can occur at any time during ICI therapy. Moreover, some studies have reported that autoimmune side effects can also occur, even after discontinuation of ICI therapy.

immune checkpoint inhibitors (ICIs) has dramatically changed the natural history of several cancer types; consequently, the clinical importance and use of immunotherapies have skyrocketed.

ICI therapy utilizes antibodies that target specific molecules involved in the signaling of tumor-related suppression of cytotoxic T lymphocytes. ICI therapy was initially used with robust evidence of clinical benefit in melanoma and non-small cell lung carcinoma and consequently approved for several other tumors (3). As the efficacy of ICI therapy corresponds to the mutational burden of the cancer, the U.S. Food and Drug Administration (FDA) approval was based for the first time on only the presence of specific mutations, regardless of tumor site or histologic type, further expanding the role of ICI therapy as one of the main alternatives for cancer treatment (4).

An essential tool for cancer management, imaging has also been impacted by ICI therapy, including adaptations in the consolidated criteria for assessment of cancer response (eg, Response

Evaluation Criteria in Solid Tumors [RECIST]), as well as increased demands for identifying a new spectrum of immune-related adverse events (irAEs) with diagnostic imaging (5). New imaging approaches for ICI therapy evaluation, such as a modified RECIST 1.1 for immune-based therapeutics (iRECIST), have been applied to overcome interpretative pitfalls in ICI-specific scenarios like pseudoprogression and hyperprogression. However, these techniques are mainly based on morphologic imaging, with its well-known advantages and limitations. In this scenario, PET—particularly fluorodeoxyglucose (FDG) PET—can provide valuable discriminative power regarding oncologic response and also aid in prognostication and early detection of irAEs. As a metabolism-based imaging technique, FDG PET allows detection of tumor activity or viability or irAEs with higher sensitivity and can show early tumor functional changes in response to therapy.

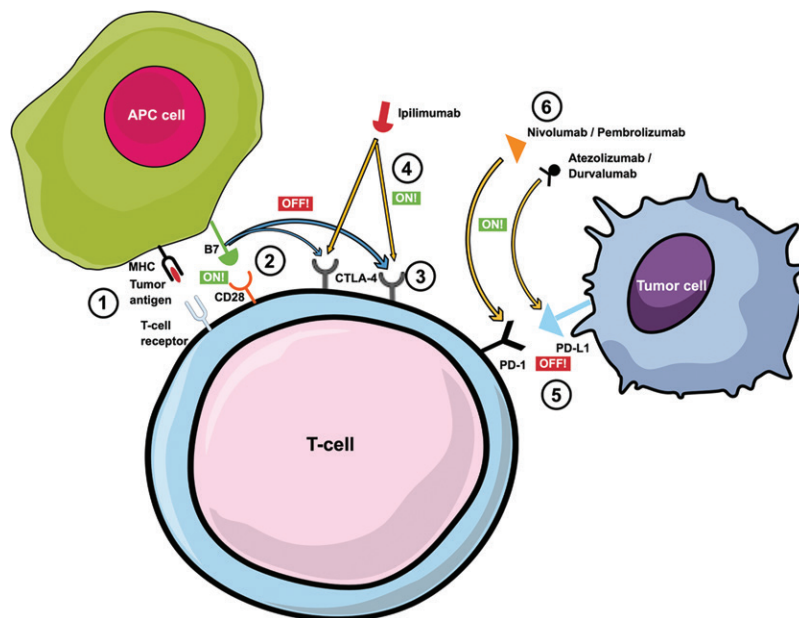
This article aims to comprehensively review the response assessment criteria for ICI therapy with imaging, from morphologic-based to metabolic-based and mixed criteria. It also addresses examples of irAEs from the perspective of FDG PET as a valuable imaging modality to improve current practice in this area.

Overview of Immunotherapy: Mechanism, Indication, and Available Drugs

Modulating the immune system is a long-term strategy to treat cancer. The first record of this approach dates to the late 19th century, when Coley's toxin was used to induce responses to various tumors (6). In the late 20th century, numerous trials tested various strategies, such as vaccines, cytokines, and immune-stimulating agents. This effort led to a few FDA approvals, including sipuleucel-T for prostate cancer (7) and interferon and interleukin-2 for treating kidney cancer and melanoma (8). These agents commonly focused on enhancing induction of the immune system but led to responses in a minority of patients.

More recently, the discovery of immune checkpoints led to a revolution in cancer immunotherapy treatments. In summary, immune checkpoint activation prevents the host immune system from reacting to tumor cells, which are recognized as foreign on the basis of neoantigen expression (Fig 1) (9,10). Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) checkpoint is dominant at the lymph node level, while programmed cell death protein 1 (PD-1) prevents responses mainly at the tumor site (11,12). ICIs are monoclonal antibodies that disrupt the interaction of CTLA-4 and PD-1 with their respective ligands, thereby reactivating the adaptive immune response against cancer.

Figure 1. Mechanism of action of immunotherapeutic agents. 1, An antigen-presenting cell (APC) presents tumor antigen to a T cell. 2, Costimulatory bonding between B7 (APC surface) and CD28 (T-cell surface) activates the T cell. 3, T-cell activation increases expression of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which outcompetes CD28, inactivating the T cell (negative feedback). 4, Ipilimumab binds to CTLA-4, and the T cell becomes activated. 5, The programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) immune checkpoint leads to downregulation of T-cell function. 6, Sites of action of the PD-1/PD-L1 inhibitors. MHC = major histocompatibility complex.



Checkpoint Inhibitors Approved by the FDA as of January 2020

Drug	Target	Approved Use (FDA)
Ipilimumab	CTLA-4	Advanced tumors: melanoma, RCC
Nivolumab	PD-1	Advanced tumors: melanoma, NSCLC, RCC, urothelial carcinoma, classic Hodgkin lymphoma, HNSCC, SCLC, HCC, dMMR colorectal cancer Adjuvant: melanoma
Pembrolizumab	PD-1	Advanced tumors: melanoma, NSCLC, HNSCC, urothelial carcinoma, classic Hodgkin lymphoma, RCC, dMMR tumors, gastric cancer, PMLBCL, Merkel cell carcinoma, cervical cancer, SCLC esophageal cancer, endometrial cancer Adjuvant: melanoma Localized: NMIUC
Cemiplimab	PD-1	Cutaneous squamous cell carcinoma
Durvalumab	PD-L1	Advanced tumors: urothelial carcinoma Stage III: NSCLC
Atezolizumab	PD-L1	Advanced tumors: urothelial carcinoma, NSCLC, SCLC
Avelumab	PD-L1	Advanced tumors: urothelial carcinoma, Merkel cell carcinoma, RCC

Source.—Reference 14.

Note.—CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, dMMR = defective mismatch repair, FDA = U.S. Food and Drug Administration, HCC = hepatocellular carcinoma, HNSCC = head and neck squamous cell carcinoma, NMIUC = non-muscle-invasive urothelial cancer, NSCLC = non-small cell lung cancer, PD-L1 = programmed cell death ligand 1, PD-1 = programmed cell death protein 1, PMLBCL = primary mediastinal large B-cell lymphoma, RCC = renal cell carcinoma, SCLC = small cell lung cancer.

It is important to note that despite inhibition of checkpoints, other components are required for an effective antitumor response, including tumor antigenicity (neoantigens), effective T-cell infiltration, and an immune-responsive microenvironment.

The first regulatory approval of a checkpoint inhibitor was obtained for ipilimumab for advanced melanoma. These agents were considered breakthroughs in 2013 (13). In 2014, the FDA first approved an anti-PD-1 agent, pembrolizumab, for advanced melanoma. Subsequently, there has been a surge in new indications for different PD-1 and

programmed cell death ligand 1 (PD-L1) inhibitors (Table).

The development of checkpoint inhibitors is characterized by a short timeline, preferential access to FDA fast-track programs, and therapeutic success, even in early trials (15). Overall, checkpoint inhibitors were first approved for a variety of advanced tumors in later lines of therapy. Most of these drugs were further tested as first-line therapies, rendering additional approvals. We are currently observing strategies using checkpoint inhibitors in combination therapies and also in

the early phases of the disease, as neoadjuvant or adjuvant therapies (16).

Many challenges are present in this new era of cancer immunotherapy. A substantial number of patients still do not derive benefit from checkpoint inhibitors. Hence, developing biomarkers of treatment response and resistance is fundamental for appropriate patient selection (17).

Response Assessment Criteria

Overview

Imaging-based therapeutic response assessment has been used for years to predict disease progression and patient outcomes earlier than clinical end points (18). While imaging biomarkers provide qualitative data, they also provide quantitative data—from different imaging modalities such as CT, MRI, and PET—to objectively measure biologic processes (19). The major role of imaging is to identify nonresponders to treatment who would benefit from a change in therapeutic management at the appropriate time. In this context, several imaging criteria based on morphologic, functional, molecular, and disease-specific biomarkers have been proposed to standardize evaluation of treatment responses (19,20). More recently, treatment-specific response evaluation guidelines have also emerged (21).

The best imaging criteria are those that are available, practical, and reproducible; have good acceptance from referring physicians; and correlate well with disease-free and overall survival. From this perspective, the morphologic criteria—such as those of the World Health Organization (WHO) and Southwest Oncology Group (SWOG) and the two versions of RECIST criteria—are the most commonly used (19). RECIST 1.1 criteria are widely adopted in clinical trials and represent the prototype of the morphologic criteria. These criteria rely on changes in tumor size to categorize the disease response to cytotoxic chemotherapeutic agents.

RECIST 1.1 defines how to measure and count target lesions, assess bone and cystic lesions, and objectively confirm progressive disease (22). These criteria incorporated a functional biomarker—FDG PET/CT—for the first time, which was used to differentiate viable from necrotic tumors as an adjunct marker of disease progression (23). However, RECIST 1.1 does not address several issues, such as possible transient increase in the volume of a responding tumor. It also does not consider the change in nature (but not in size) of a target lesion, such as the appearance of necrosis in a solid lesion or a bone lesion turning from lytic to sclerotic, and does not define the treatment modality.

New criteria have been proposed to overcome these limitations and assess responses to immuno-

therapy. In 2009, the Immune-related Response Criteria (irRC) were first adapted from the bidimensional WHO criteria (24); they were later adapted to the unidimensional RECIST and called irRECIST in 2013 (25). These criteria defined four imaging outcomes associated with favorable survival, including initial increase in the tumor burden or even the appearance of new lesions as patterns of response. In practice, these criteria included new target lesions in the tumor burden and required a confirmatory assessment at least 4 weeks ahead. In 2017, the RECIST Working Group developed a modified RECIST 1.1 for immune-based therapeutics, termed iRECIST. The major change was introduction of the concept of resetting the bar if disease progression is followed by tumor shrinkage at the next assessment (26).

Functional criteria have also played a supporting role in oncologic assessment of therapeutic response. The European Organization for Research and Treatment of Cancer (EORTC) criterion was designed to use FDG PET to evaluate treatment responses, using the percentage change in the maximum standardized uptake value (SUV_{max}) of a single lesion to determine the pattern of response (27). This criterion could be applied to noncytotoxic agents.

Later, the PET Response Criteria in Solid Tumors (PERCIST) were proposed and included anatomic imaging biomarkers, standardization of imaging acquisition and measurements, and an increase in the maximum number of measurable lesions to five (28). Owing to the low availability and high cost of PET/CT, use of PERCIST is not as widespread as that of RECIST. Therefore, more clinical data are needed to assess the prognostic value of PERCIST (29).

Adaptations were made to functional criteria to assess immunotherapy responses with FDG-PET/CT. At least three different criteria have been proposed, based on analysis of melanoma and lung cancer patients: the PET/CT Criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy (PECRIT) (30), PET Response Evaluation Criteria for Immunotherapy (PERCINT) (31), and immune PERCIST (iPERCIST) (32). PECRIT is a combination of RECIST 1.1 and EORTC, and these criteria combine some features of EORTC, RECIST 1.1, PERCIST, and iRECIST. PECRIT differs mainly in the number and size of new lesions for defining progressive disease and the ideal time point for imaging. An overview of the main morphologic and functional criteria is summarized in Figure 2.

Moreover, many other imaging criteria are available for monitoring different biologic processes, specific tumors, and novel treatments. For assessing lymphoma patients after treatment, the

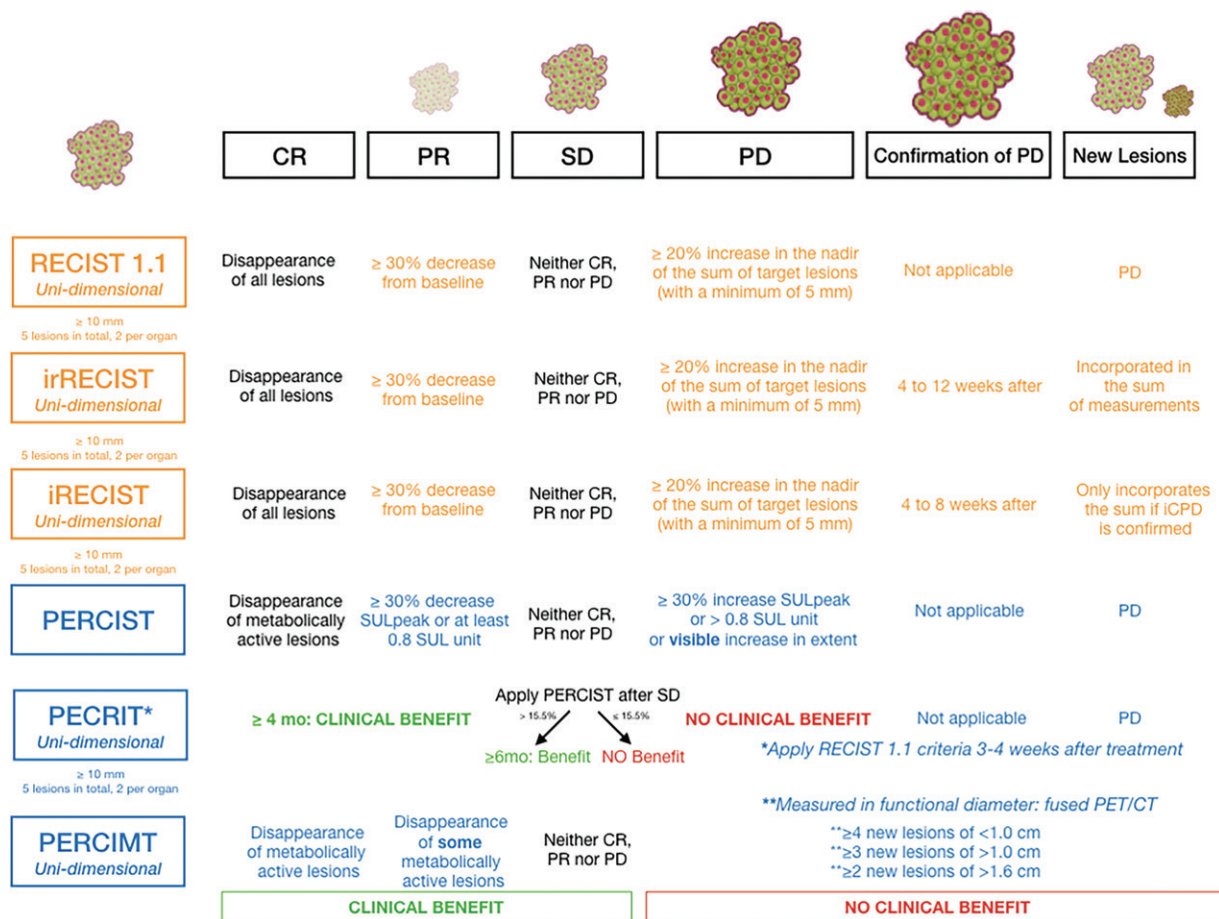


Figure 2. Different criteria for imaging assessment of response in solid tumors. CR = complete response, iCPD = “immune” confirmed PD, iRECIST = modified RECIST 1.1 for immune-based therapeutics, irRECIST = immune-related RECIST, PD = progressive disease, PECRIT = PET/CT Criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy, PERCINT = PET Response Evaluation Criteria for Immunotherapy, PERCIST = PET Response Criteria in Solid Tumors, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease, SUL = standardized uptake value (SUV) corrected for lean body mass.

Lugano Classification is a well-established method based on tumor uptake (SUV_{max}) at FDG PET/CT, in comparison with the glycolytic metabolism of physiologic organs (mediastinal blood pool and liver). A refinement was proposed for patients after immunotherapy (Lymphoma Response to Immunomodulatory Therapy Criteria [LYRIC]) and included a new category, the indeterminate response, recognizing the possibility of a delayed response and an immune-mediated flare that requires confirmation imaging within 12 weeks (33).

Adjustments have also been made for other tumors to include specific patterns of response, such as cystic degeneration, necrosis, hemorrhage, and cavitation. Some examples are gastrointestinal stromal tumors treated with imatinib (Choi Criteria), hepatocellular carcinoma (European Association for the Study of the Liver [EASL] guidelines and modified RECIST [mRECIST]), primary and metastatic brain tumors (Response Assessment in Neuro-oncology [RANO] Criteria), and metastatic renal cell carcinoma treated with tyrosine kinase inhibi-

tors (Size and Attenuation CT [SACT] Criteria) (20). Figure 3 exemplifies the common and peculiar patterns of response that might occur according to the tumor and the treatment.

Regardless of the adopted imaging criteria, the most important information in oncologic assessment of therapeutic response is definition of one of the four possible patterns: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), with some possible adaptation according to the antineoplastic agent used.

Usual Patterns

Complete Metabolic Response.—There is a strong relationship between FDG uptake and the number of viable cancer cells. A reduction in FDG uptake usually denotes treatment response, which precedes changes in tumor size. Therefore, PET/CT may be used for assessing response to immunotherapy early after initiating treatment to predict efficacy, at midtreatment, and at the end

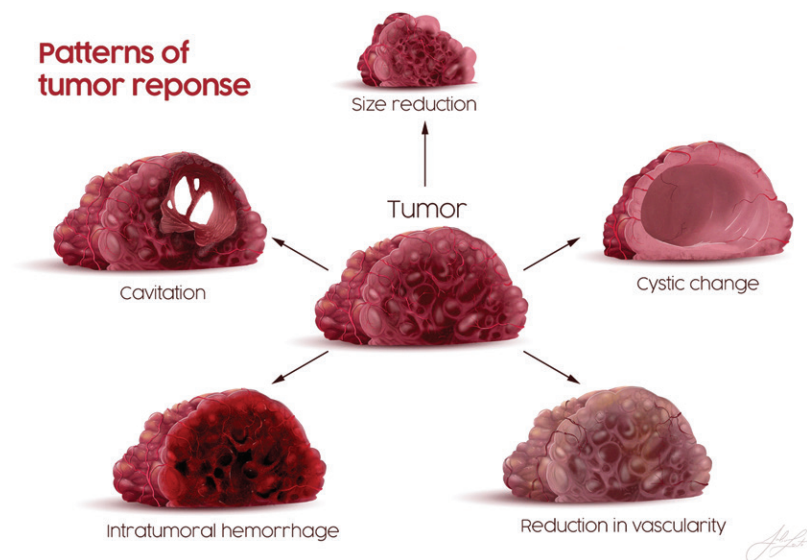


Figure 3. Various standards of response after use of immunotherapeutic agents. Different morphologic patterns may emerge and represent response even in the absence of lesion volumetric changes.

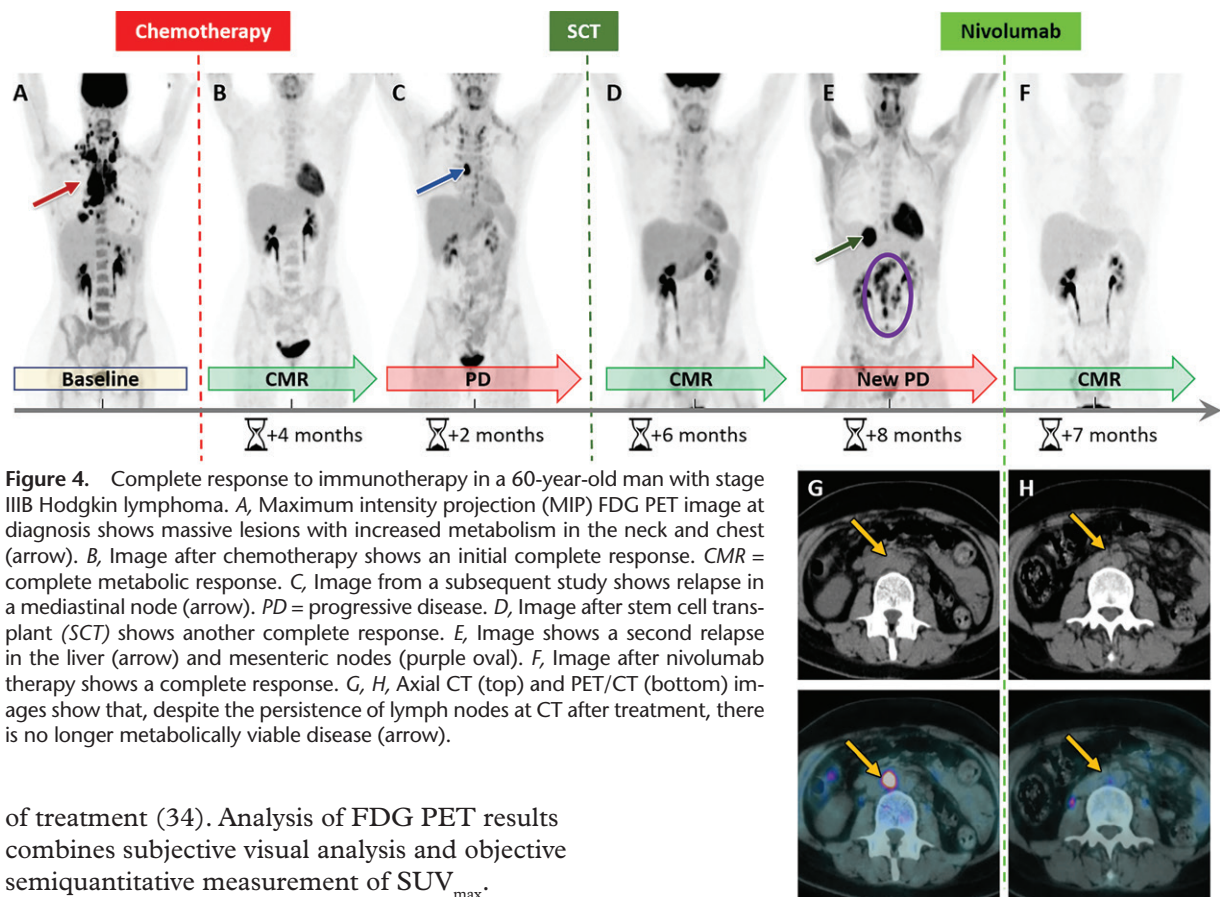


Figure 4. Complete response to immunotherapy in a 60-year-old man with stage IIIB Hodgkin lymphoma. *A*, Maximum intensity projection (MIP) FDG PET image at diagnosis shows massive lesions with increased metabolism in the neck and chest (arrow). *B*, Image after chemotherapy shows an initial complete response. CMR = complete metabolic response. *C*, Image from a subsequent study shows relapse in a mediastinal node (arrow). PD = progressive disease. *D*, Image after stem cell transplant (SCT) shows another complete response. *E*, Image shows a second relapse in the liver (arrow) and mesenteric nodes (purple oval). *F*, Image after nivolumab therapy shows a complete response. *G, H*, Axial CT (top) and PET/CT (bottom) images show that, despite the persistence of lymph nodes at CT after treatment, there is no longer metabolically viable disease (arrow).

of treatment (34). Analysis of FDG PET results combines subjective visual analysis and objective semiquantitative measurement of SUV_{max} .

Disappearance of FDG uptake in all lesions (whether measurable or not, and no new lesions) means a complete metabolic response, regardless of a change in tumor size (Fig 4). A baseline study is required for future comparisons. The first treatment response evaluation is usually performed after two or three cycles of treatment (8 or 9 weeks). Follow-up studies are recommended every 6–12 weeks, depending on the frequency of treatment visits and the duration of treatment (Fig 5) (26,35).

Partial Metabolic Response.—Reduction of FDG uptake in metastatic lesions is related to a partial response (Fig 6). The optimal threshold is controversial, varying from 15% to 30%, according to the EORTC and PERCIST recommendations (29). This measurement can be made using SUV_{mean} , normalized to body surface area, or SUV_{peak} , normalized to lean body mass.

Figure 5. Immunotherapy-related thyroiditis in a 58-year-old man with a history of shoulder melanoma treated with resection and radiation therapy. He underwent FDG PET/CT for restaging. *A*, MIP FDG PET image shows emergence of hypermetabolic portocaval lymph node enlargement (red oval). *B*, Image after pembrolizumab therapy shows development of immunotherapy-related thyroiditis (blue arrow) with bilateral reactive cervical lymph nodes (red arrows) and a partial response (PR) in the malignant lesions (purple oval). *C*, *D*, Images from subsequent studies show a complete metabolic response (CMR) in the neoplastic lesions and resolution of the thyroiditis.

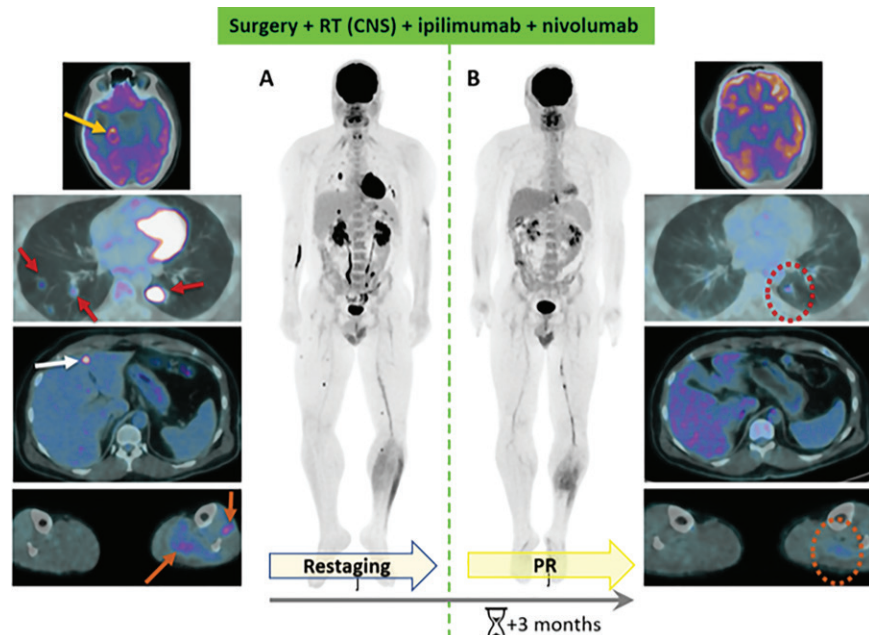
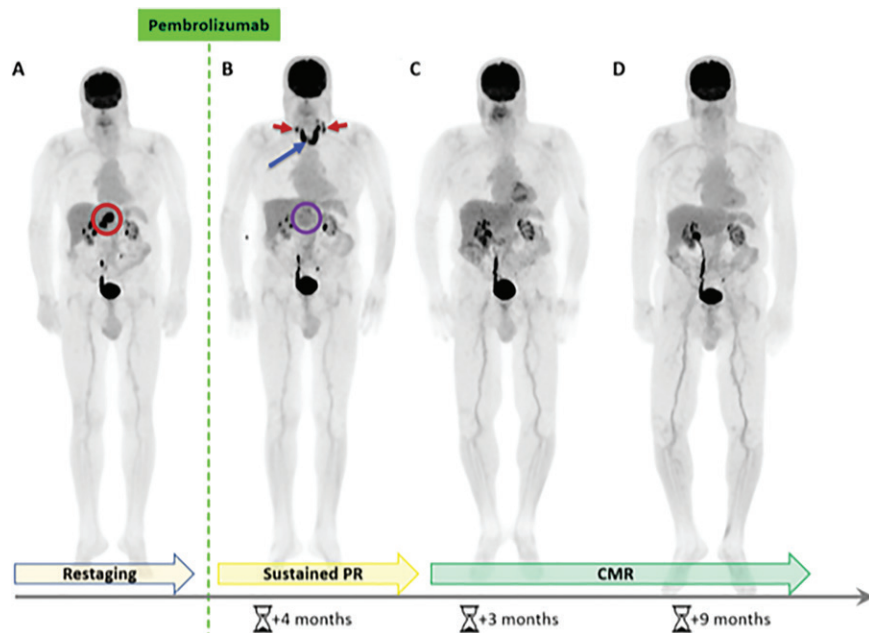


Figure 6. Multiple sites of response to immunotherapy in a 49-year-old man with a previously resected metastatic left arm melanoma. He underwent FDG PET/CT for restaging. *A*, MIP FDG PET image (right) and axial PET/CT images (left) show a right temporal lobe metastasis (yellow arrow), multiple pulmonary nodules (red arrows), a hepatic metastasis (white arrow), and muscular involvement in the left leg (orange arrows). *B*, Axial FDG PET/CT images for response assessment, obtained after resection and radiation therapy (RT) of the central nervous system (CNS) lesion and treatment with ipilimumab and nivolumab, show only slight metabolism in one pulmonary nodule with significant volume reduction (red dotted circle) and reduction of metabolism in the left lower limb lesion (orange dotted circle). The brain and liver metastases both demonstrate a complete metabolic response. PR = partial response.

An increase in morphologic size of greater than 30% would indicate progressive disease according to PERCIST, regardless of the change in FDG uptake. This may not be a concern during the first response assessment for patients undergoing immunotherapy. Inflammatory changes are a common

feature at the beginning of this treatment and would contribute to lesion enlargement. Interestingly, according to RECIST, even nontarget lesions such as bone metastases might be measurable with PET and then count for response assessment, overcoming a limitation of the anatomic criteria (Fig 7).

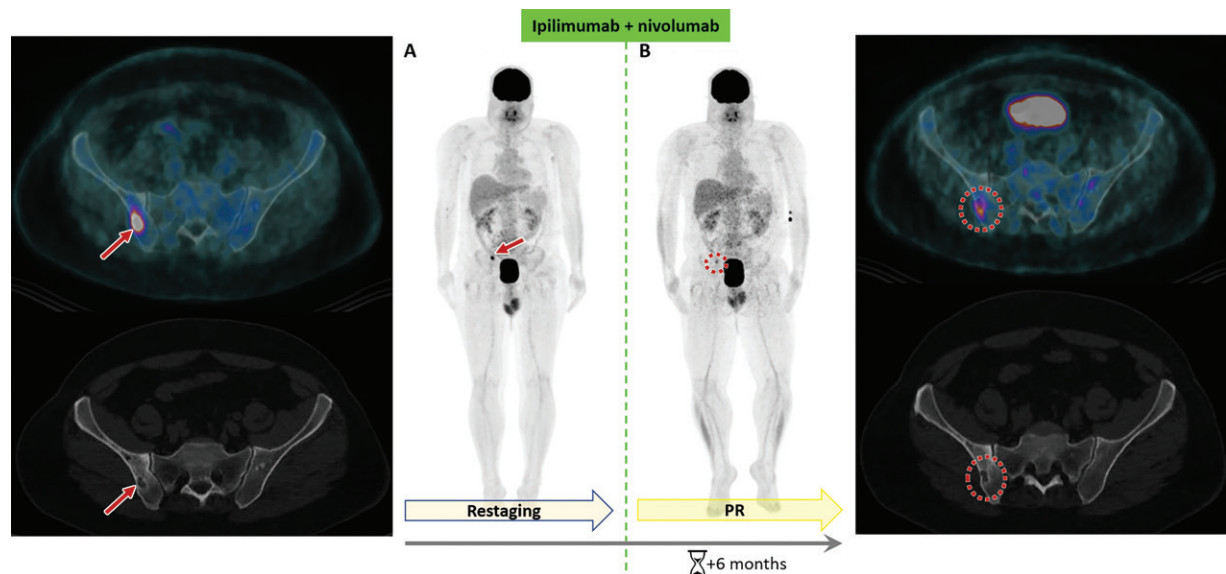


Figure 7. Bone lesion with a partial response (PR) to immunotherapy in a 50-year-old man with metastatic melanoma of unknown primary site previously treated with lumbar spine radiosurgery and whole-brain radiation therapy. He underwent FDG PET/CT for restaging. A, FDG PET image (right) and axial PET/CT (top left) and CT (bottom left) images show a metastatic bone lesion in the right ilium (arrow). Ipilimumab therapy was started, followed by nivolumab therapy; 6 months later, FDG PET/CT was performed for restaging and response assessment. B, FDG PET image (left) and axial PET/CT (top right) and CT (bottom right) images show a partial metabolic response (red dotted circle).

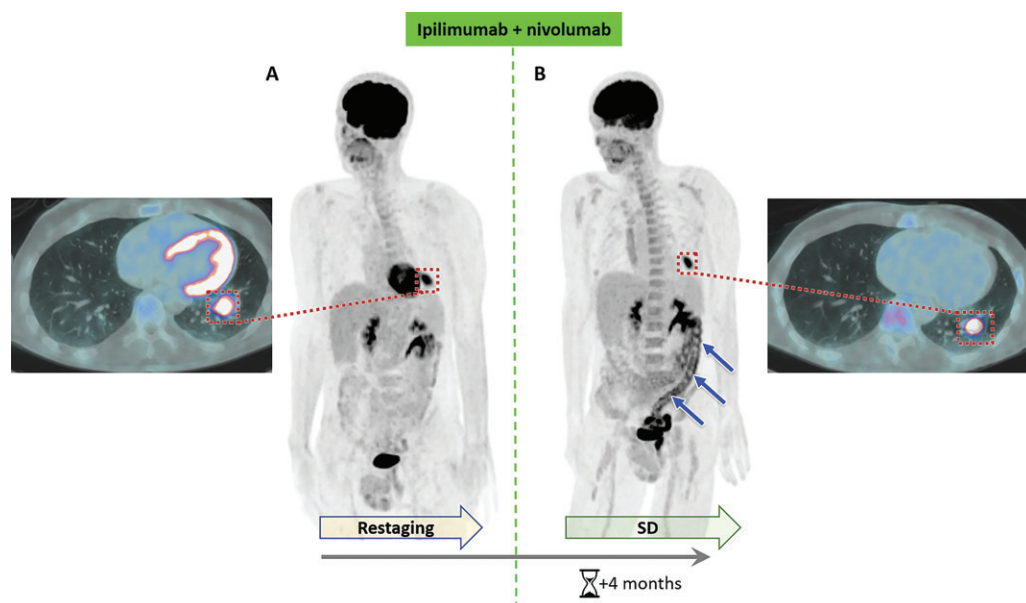


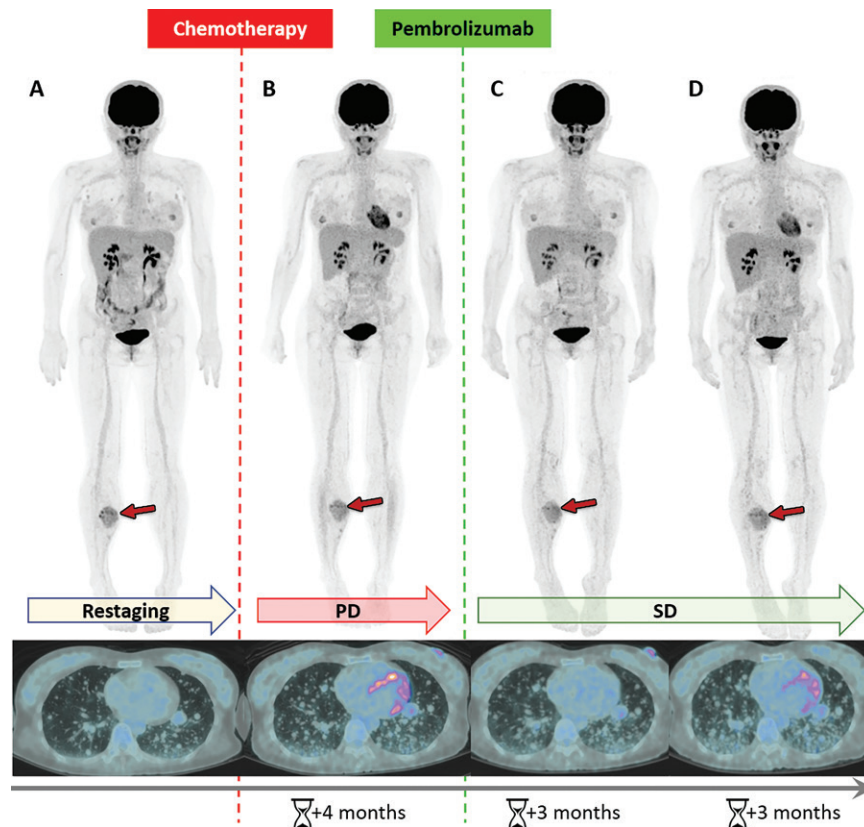
Figure 8. Stable disease with onset of immunotherapy-induced colitis in a 57-year-old man with a history of resected right dorsal melanoma 4 years earlier. He underwent FDG PET/CT for restaging. A, MIP FDG PET (right) and axial PET/CT (left) images show a left lower lobe metastasis (red dotted square). Ipilimumab therapy was begun, followed by nivolumab therapy. B, MIP FDG PET (left) and axial PET/CT (right) images show that stable disease (SD) was maintained (red dotted square) despite the onset of immunotherapy-induced colitis (blue arrows).

Note that both complete and partial metabolic responses may occur after one or more instances of iRECIST-unconfirmed progressive disease (iUPD) but not after iRECIST-confirmed progressive disease (iCPD).

Stable Disease.—Stable disease is characterized as an increase or decrease in tumor burden that

does not qualify as progressive disease or partial response (Fig 8) (24). In the context of immunotherapy, stable disease is defined as a distinct pattern of disease response that might be followed by a slow decline in total tumor burden. Patients who present with stable disease after immunotherapy are considered to have received a clinical benefit (31). This stable disease before a decrease

Figure 9. Stable disease after immunotherapy in a 38-year-old woman with metastatic alveolar sarcoma. She underwent FDG PET/CT for staging. *A*, MIP FDG PET (top) and axial PET/CT (bottom) images show alveolar sarcoma of the right leg (arrow) and lung metastases. *B*, Images for response assessment after chemotherapy show metabolic stability of the leg lesion (arrow) but slight increase in number and size of the pulmonary nodules. *PD* = progressive disease. *C*, *D*, Images after immunotherapy was started show maintenance of stable disease (*SD*). Arrow = leg lesion.



in tumor burden may reflect the interval in which the immune system activates T cells to control the tumor (36) (Fig 9).

Progressive Disease.—Evaluation of morphologic tumor responses is mostly unaffected by RECIST 1.1 (28). The most important change in immune-related response criteria (such as iRECIST) is implementation of different time points for assessing early progressive disease. Progressive disease is characterized by the following metabolic parameters: (a) increase in FDG uptake (without considering tumor size) of 25%–30%, according to EORTC and PERCIST recommendations (Fig 10) (29); (b) visible increase in the extent of fluorine 18 (^{18}F)–FDG tumor uptake; or (c) appearance of new ^{18}F –FDG uptake in metastatic lesions (Fig 11).

To identify functional criteria at the second time-point evaluation after early PD, iPERCIST (an adaptation of PERCIST) was proposed (32). These new criteria incorporated two new patterns: unconfirmed metabolic progression (uMPD) and confirmed progressive metabolic disease (CPMD). Although iPERCIST requires further validation in large prospective studies, it follows the same premises as iRECIST-unconfirmed progressive disease (iUPD) and iRECIST-confirmed progressive disease (iCPD).

In essence, uMPD (similar to iUPD of iRECIST) requires follow-up with interval studies

to confirm disease status. A lesion with increased FDG uptake or the appearance of a new lesion at the first PET evaluation 8 weeks after starting therapy is considered to be a uMPD/iUPD. Therefore, a second evaluation after 4–8 weeks is required for CPMD (similar to iCPD at iRECIST) or to observe different possible responses.

These may include the following: (a) maintenance of iUPD/uMPD status if there is no uptake change at the follow-up study or if there is a decrease in lesion uptake when compared with the second time-point study; (b) stable disease if an increase or decrease in tumor burden insufficient to qualify as progressive disease or partial response is observed; or (c) partial response if there is a 30% or greater decrease in the lesion's uptake when compared with the baseline study (Fig 12). Although it is essential to compare findings with those of the previous examination, the guidelines recommend comparison with the baseline study to decide the current pattern of response at follow-up studies after an iUPD (26,28,37,38).

Unusual Patterns

New and unusual response patterns appeared after introducing ICIs as a treatment modality for oncology patients, namely pseudoprogression (a brief illusory increase in tumor burden, succeeded by response) and hyperprogression (acceleration of disease). These new patterns were

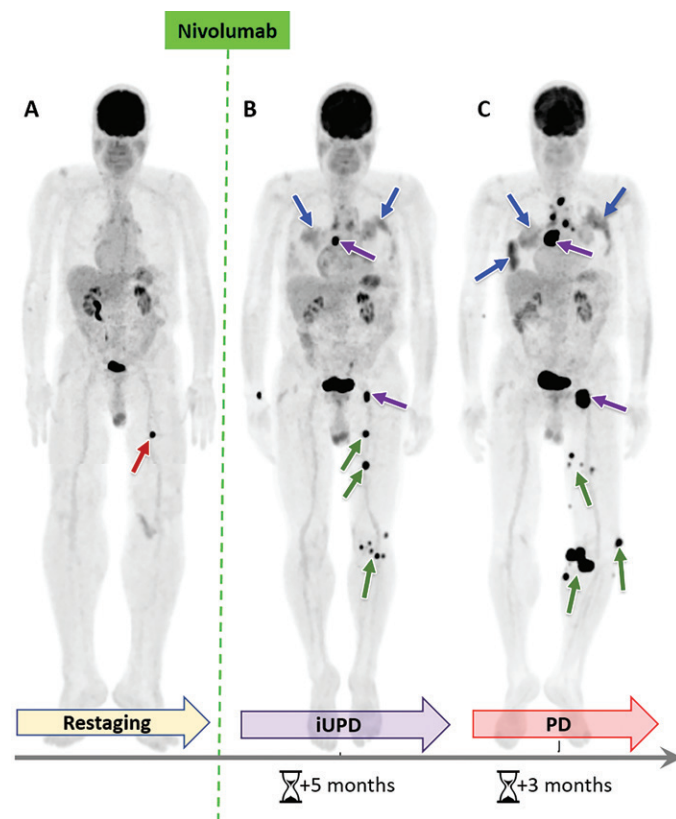


Figure 10. Progression of disease after immunotherapy in a 73-year-old man with a left calf melanoma previously treated with resection and chemotherapy. He underwent FDG PET/CT for restaging. *A*, MIP FDG PET image shows a subcutaneous nodule (arrow) in the left lower limb. Nivolumab therapy was begun. *B*, Image for response assessment shows the appearance of multiple metastatic lesions, especially subcutaneous nodules in the left lower limb (green arrows) and inguinal and mediastinal lymph nodes (purple arrows). Also note the diffuse pulmonary hypermetabolism (blue arrows) related to immunotherapy-mediated pneumonitis. *iUPD* = iRECIST-unconfirmed progressive disease. *C*, Image after continuation of nivolumab therapy shows confirmed progressive disease (PD).

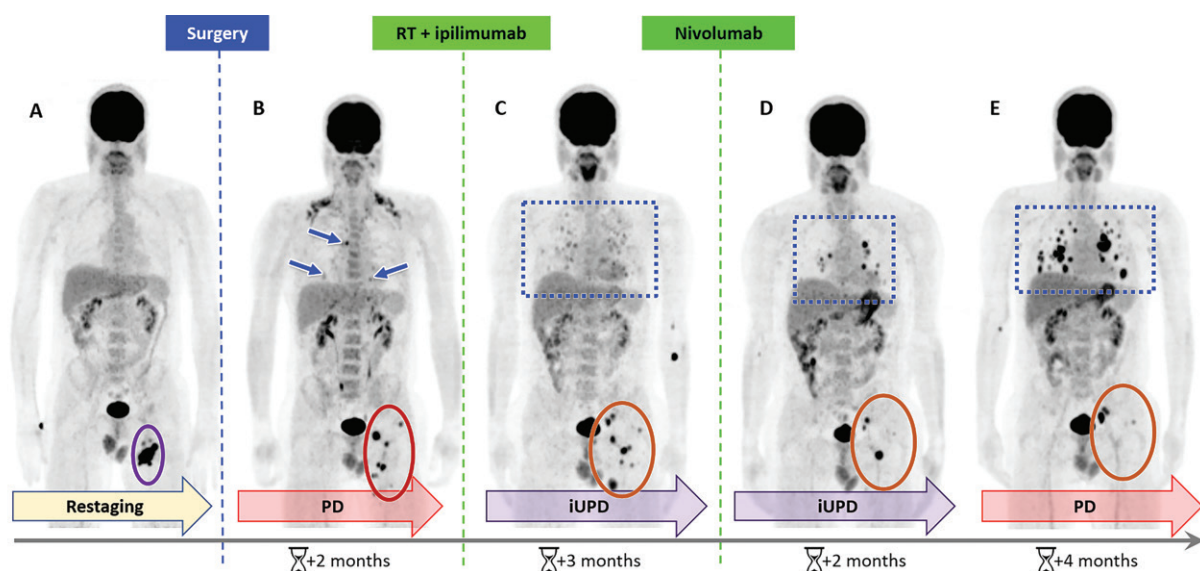


Figure 11. Immune-unconfirmed progressive disease (iUPD) followed by progressive disease (PD) after immunotherapy in a 45-year-old man with a history of left hallux melanoma treated with resection, homolateral inguinal lymphadenectomy, and adjuvant interferon. He underwent FDG PET/CT for restaging. *A*, FDG PET image shows secondary lesions in the left thigh (purple oval), which were subsequently resected. *B*, Follow-up image shows new lesions in the left thigh (red oval) and onset of metastatic pulmonary nodules (arrows). Ipilimumab and left thigh radiation therapy (RT) were initiated. *C*, Image for response assessment shows increased tumor burden in the pulmonary (dotted blue rectangle) and thigh (orange oval) lesions, in keeping with iUPD. *D*, *E*, After the immunotherapeutic agent was changed to nivolumab, images from subsequent studies show that the iUPD changed to PD in the same sites.

due to the biologic mechanism of drug action and were found to differ from those established after cytotoxic chemotherapy or radiation therapy (39,40). Over the years, it was noticed that a functional response to immunotherapy usually

precedes a morphologic response; therefore, morphologic criteria are most likely inadequate for assessment of pseudoprogression and hyperprogression—situations that usually require more time to achieve a final clinical effect.

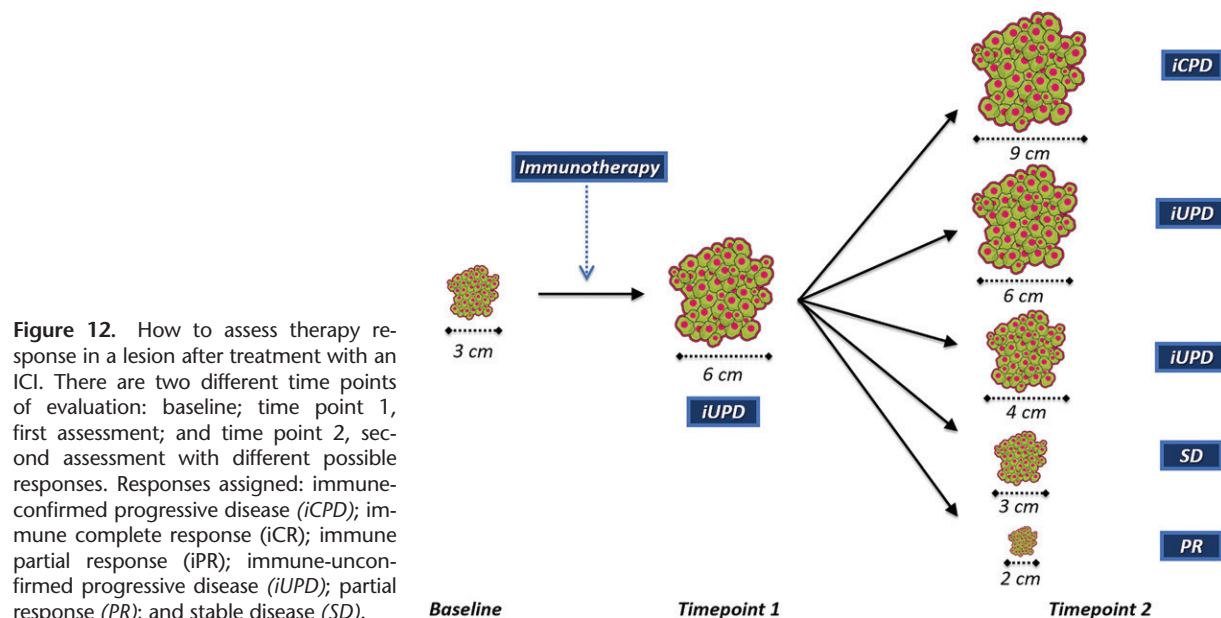
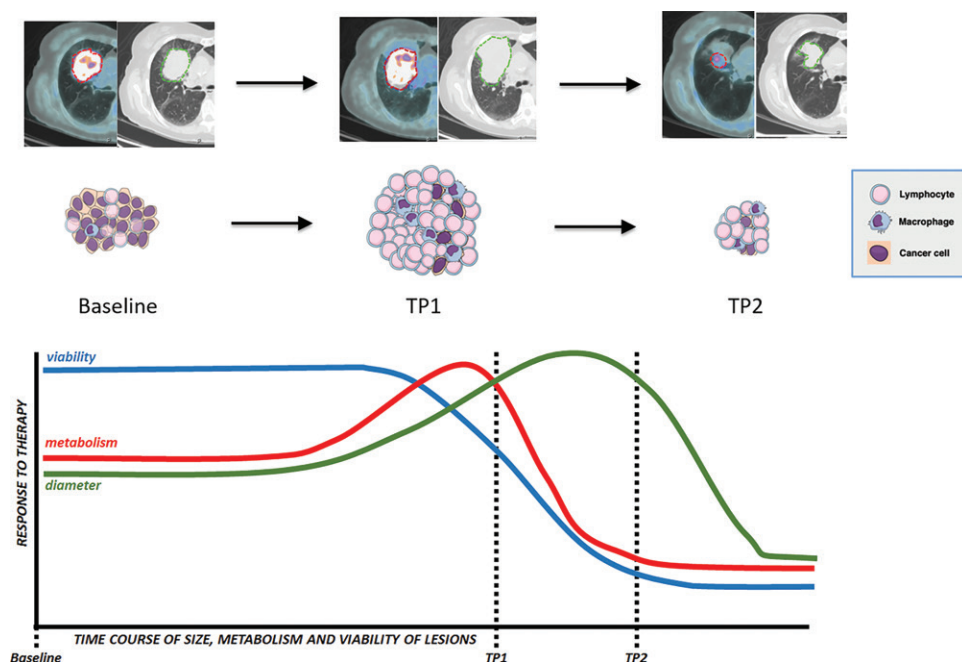


Figure 13. Pseudo-progression. *TP1* = time point 1, *TP2* = time point 2. Top: Axial FDG-PET/CT (left) and CT (right) images show pseudo-progression. Bottom: Corresponding curves of biologic changes in tumor viability and metabolism over time.



Pseudoprogression.— ^{18}F -FDG PET/CT is a useful tool for assessing systemic cancer treatment at different time points during therapy and aids in differentiating pseudoprogression from true progression. A reduction in tumor diameter might be postponed to some extent, over changes in tumor metabolism and changes in tumor viability (Fig 13). In this respect, some studies have suggested use of volumetric indexes derived from ^{18}F -FDG PET, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG).

MTV is a quantitative form of measurement of tumor burden that expresses the total volume of tumor lesions with increased metabolic activity—that is, the volume of tumor lesions exhibiting an SUV

over a certain threshold. On the other hand, TLG estimates how much glucose is consumed by the totality of tumor lesions present in an individual. Thus, TLG is generated by the product of MTV and the mean SUV of the volume: $\text{TLG} = \text{MTV} \times \text{SUV}_{\text{mean}}$. MTV and TLG are frequently thought to represent better prognostic tools than simple metabolic measurements such as SUV_{max} , as they reflect the tumor burden more reliably (41,42).

Pseudoprogression is defined as an illusory increase in metabolic tumor burden—varying from 25% to 30% (Fig 13)—or the appearance of new lesions (Fig 14) before occurrence of a subsequent decrease or stability (43,44). This peculiarity is properly described in the context of ICI

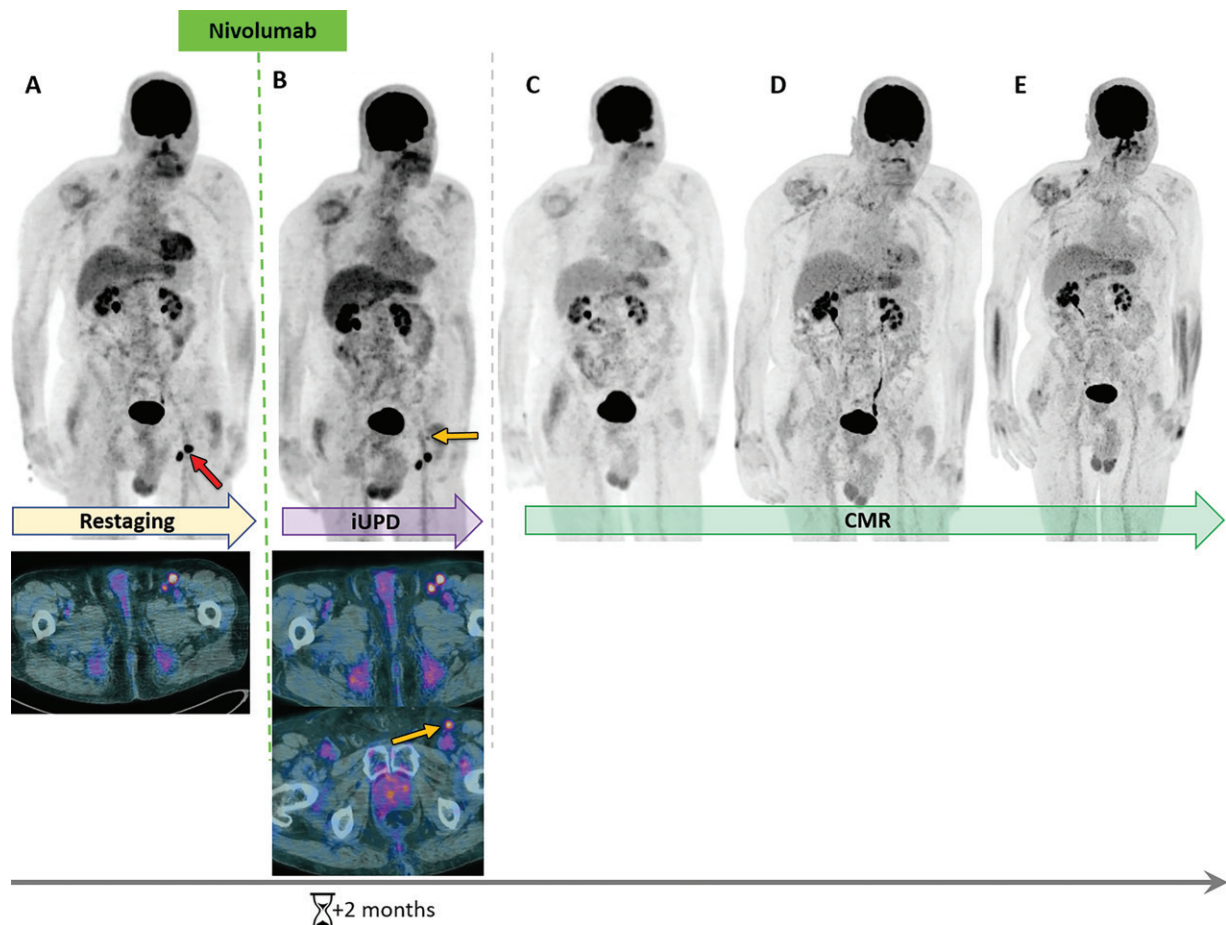


Figure 14. Immune-unconfirmed progressive disease (*iUPD*) followed by a complete response after immunotherapy in a 62-year-old man with a high-risk melanoma of the left leg. He underwent restaging with FDG PET/CT after resection. *A*, MIP FDG PET (top) and axial FDG PET/CT (bottom) images show a relapse in the inguinal nodes (arrow). *B*, Images from an interval study after nivolumab therapy show *iUPD*, with a new pelvic node (arrow). *C–E*, Images from follow-up studies show a complete and sustained response (*CMR*).

therapy, although it is also characterized in other target therapies. Pseudoprogression was first described in an estimated 2%–14% of melanoma patients after use of ipilimumab, a CTLA-4 agent (45,46), and later in other tumors (lung cancer, renal cell carcinoma, urothelial cancer [47], and bladder cancer) with use of the anti-PD-1 inhibitors nivolumab and pembrolizumab. However, these cases are much rarer (<3%) (43).

Targeted therapies, especially ICI therapy, might lead to an early increase in lesion metabolism. Those effects include immune cell infiltration into the tumor, intracellular and vasogenic edema and inflammation, and even intratumor hemorrhage due to the characteristics of the tumor's vasculature (37). All of those features could initially appear as a lesion with increased metabolism at an early response evaluation, which constitutes a requirement for follow-up with interval studies for imaging reassessment after 4–8 weeks (never more than 12 weeks—this risks decompensation to the point of being incapable of receiving salvage chemotherapy).

Hyperprogression.—Immune-related response criteria are designed to identify pseudoprogression. However, no tool has been defined for identifying hyperprogressive disease (HPD)—a new and challenging response pattern defined as a twofold or greater increase in the tumor volume growth rate during immunotherapy (Fig 15), which manifests with a worse clinical outcome (47–49). HPD status has been characterized in many tumor types (eg, melanoma, renal cell carcinoma, urothelial carcinoma, nonsquamous non-small cell lung cancer, and head and neck squamous cell carcinoma [HNSCC]). Therefore, HPD is independent of histologic type, with an incidence range of 9% in melanoma patients and 29% in patients with HNSCC (50). HPD is primarily related to use of anti-PD-1/PD-L1 agents, although it also occurs with use of anti-CTLA-4 therapy.

Some factors have previously been associated with HPD, such as older age (>65 years) (Figs 15, 16) (49), more than two metastatic lesions at baseline, and local-regional disease recurrence (Figs 16, 17). A change in therapy should always

Figure 15. Hyperprogression after immunotherapy in an 89-year-old man with clear cell renal carcinoma. MIP FDG PET images show the baseline appearance at diagnosis (A), progressive disease (PD) after nephrectomy (B), and hyperprogression after pembrolizumab therapy (C), with an important partial response (PR) after chemotherapy (D).

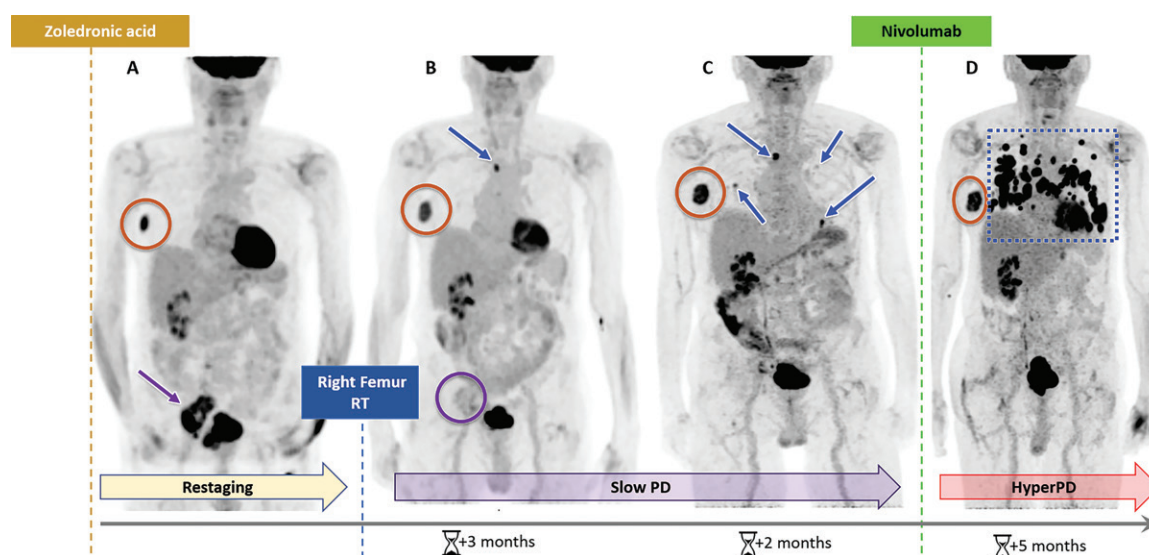
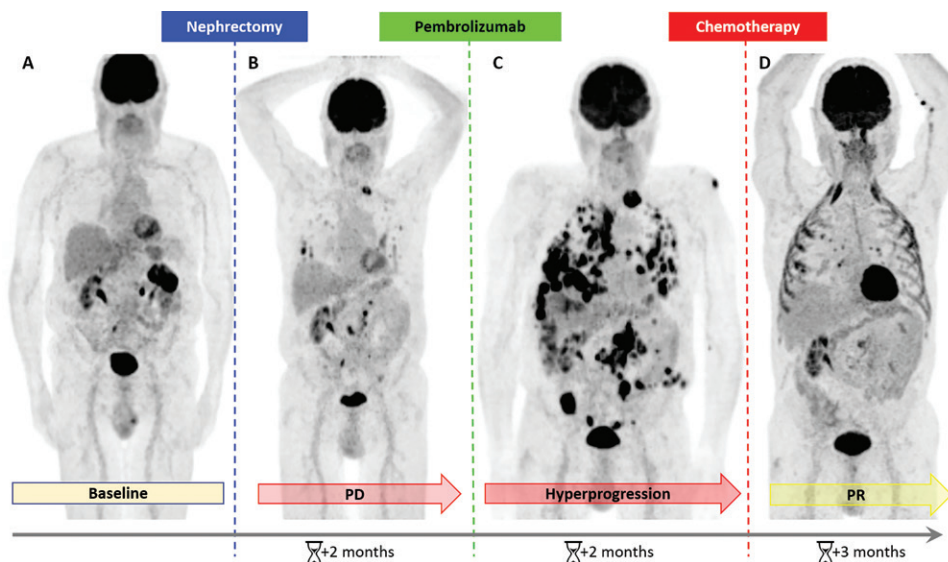


Figure 16. Hyperprogression after immunotherapy in an 80-year-old man with metastatic clear cell renal carcinoma. He underwent FDG PET/CT for restaging. A, FDG PET image shows femoral (arrow) and right axillary (orange circle) lesions. Radiation therapy (RT) to the femur was performed. B, C, Images from interval studies show substantial reduction in the metabolism of the femoral lesion (purple circle). However, there is slow systemic progressive disease (PD), with pulmonary (arrows) and right axillary (orange circle) lesions, which increased progressively over time. D, Image after nivolumab therapy shows hyperprogression (blue dotted rectangle). Orange oval = right axillary lesion.

be considered after HPD owing to the high mortality and median overall survival of 3–6 months (Fig 15). There is no current association with disease stage or poor performance at baseline in any published studies (49,50). HPD is an insufficiently investigated pattern of response, and the exact underlying pathophysiology remains unknown. Five major hypotheses have been proposed: (a) T regulatory cell expansion, (b) T-cell exhaustion, (c) modulation of protumorigenic immune subsets, (d) oncogenic pathway activation, and (e) aberrant inflammation (50).

There are no current immune-related response criteria that allow differentiation among hyper-

progression, true progression, and pseudoprogression within 8 weeks of starting treatment. This makes a second evaluation essential to avoid (a) early cessation of treatment that may eventually provide a therapeutic benefit or (b) maintaining a patient on an ineffective treatment.

Immune-related Adverse Effects

Overview

ICIs use the patient's immune system to fight against tumor cells. Blocking intrinsic downregulators of immunity can hyperactivate the immune system through T lymphocytes. Such increased

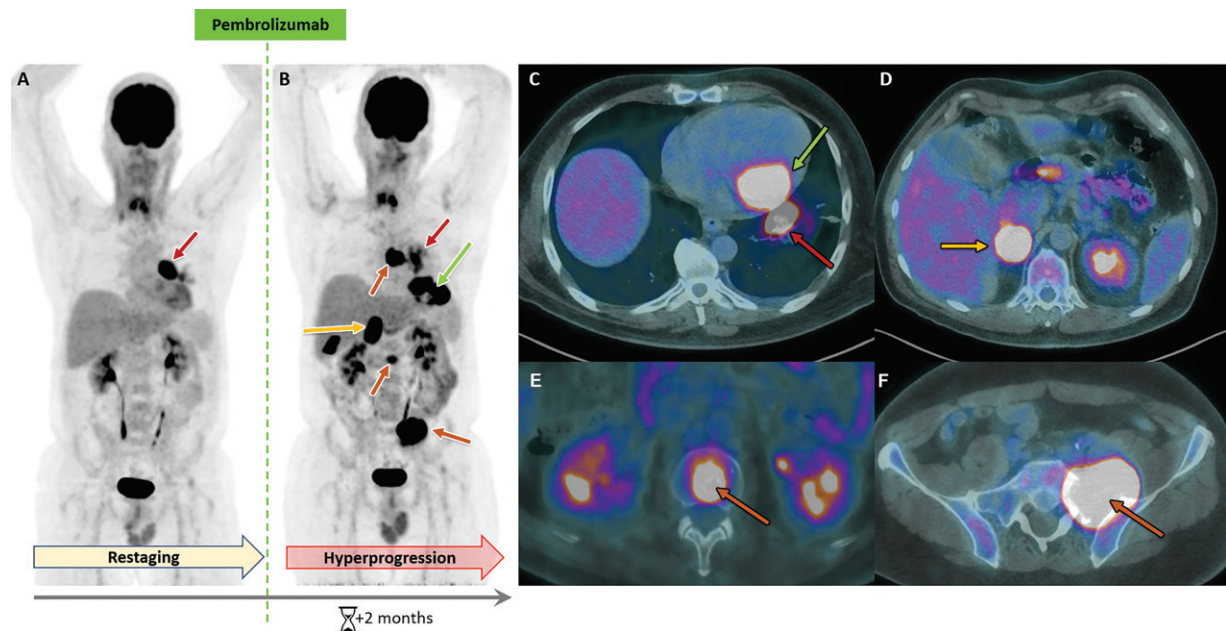


Figure 17. Hyperprogression after immunotherapy in a 50-year-old man with oropharyngeal squamous cell carcinoma. *A*, MIP FDG PET image from the restaging study shows a pulmonary metastasis (arrow). *B–F*, MIP FDG PET (*B*) and axial FDG PET/CT (*C–F*) images after pembrolizumab therapy show hyperprogression, with appearance of metastatic pulmonary (red arrows), heart (green arrows), right adrenal (yellow arrows), and bone (orange arrows) lesions. The patient died 7 months later.

immune system activity can activate T immune cells in a variety of normal tissues, causing autoimmune side effects, also known as irAEs. The precise pathophysiology underlying irAEs is not clearly understood. It is believed that immune checkpoints play a role in maintaining immunologic homeostasis; as an autoimmune process, this can potentially affect any tissue or organ in the body through inflammation.

Most irAEs are mild, but in some circumstances they can cause limitations or even be life threatening. They require discontinuation of ICI therapy and active treatment (51–53). Rapid identification of irAEs can improve patient outcome when implementing proper treatment. Although imaging findings of irAEs should be reported, these will not necessarily be associated with clinical symptoms. Nevertheless, clinicians should be alerted to their presence and should ensure close clinical monitoring.

The frequency of irAEs differs across ICI therapy schemes. Anti-CTLA-4 drugs generally cause more irAEs than anti-PD-1 or anti-PD-L1 drugs. Combined treatment with anti-CTLA-4 plus anti-PD-1 or anti-PD-L1 (which is frequently used in melanoma patients) has the highest incidence of immune side effects compared with any individual ICI therapy. A different pattern is seen with the most commonly used anti-CTLA-4 drug, ipilimumab. Ipilimumab has a clear dose-dependent association in terms of the incidence and severity of irAEs, with higher doses causing more side effects. The

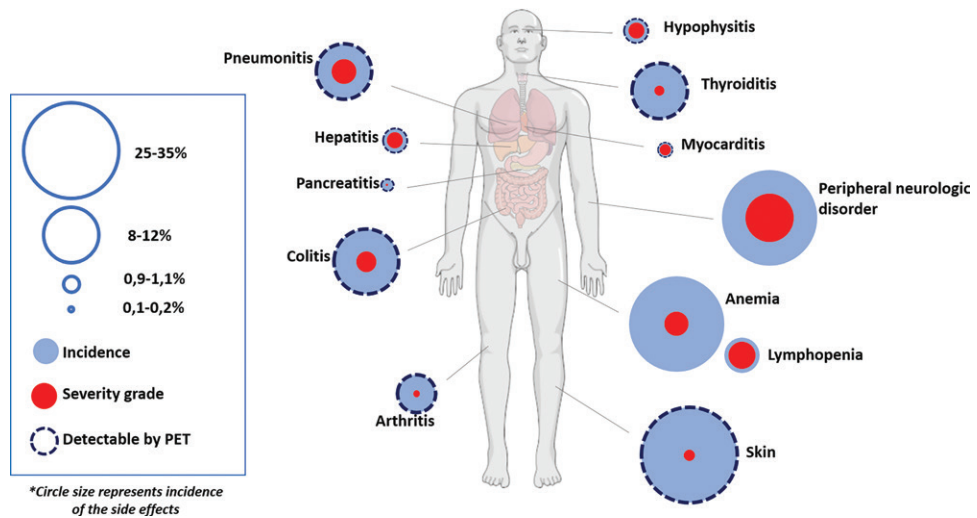
other ICI drugs do not show such dose-dependent behavior (52).

After the start of ICI therapy, irAEs commonly manifest within the first 3 months of administration for most drugs. Moreover, there is also a tendency for a temporal pattern of toxic effects to manifest after commencement of therapy: dermatologic effects are noted first (within 2–3 weeks), followed by gastrointestinal or hepatic effects (within 6–7 weeks), pulmonary effects (within 9 weeks), and endocrine-related effects (within 9–11 weeks). With anti-CTLA-4 drugs, such manifestations tend to occur somewhat earlier than with other ICIs (52,54). Despite such a pattern, any irAE can occur at any time during ICI therapy. Moreover, some studies have reported that autoimmune side effects can also occur, even after discontinuation of ICI therapy (51,53).

There is a possible positive association between irAEs and tumor response to ICI treatment (Fig 5). One rationale suggests that a greater immune system response leads to more effective antitumor activity and consequently greater autoimmunity (and toxicity). Another argument suggests that in cases of tumor response, the patient is exposed to ICI therapy for a more extended period, which could increase the rate of toxic effects over time (51,53).

As irAEs may be mistaken for metastases or tumor progression, clinicians, radiologists, and nuclear medicine physicians have to be aware of such promising therapy nuances when assessing therapy response with imaging to avoid potential pitfalls.

Figure 18. Diagram of the various possible adverse effects of immunotherapy, as well as their incidence (blue circles), severity (red circles), and detectability with PET/CT (dashed circles). The sizes of the circles reflect the incidence of toxic effects.



Although any organ or system can be affected, irAEs most commonly involve the skin, colon (gastrointestinal tract), liver, lungs, endocrine glands, and joints. Other sites are less often affected, such as the central nervous system, cardiovascular system, hematologic system, kidneys, and ocular system. Some of these organ toxic effects are clinically diagnosed and do not require further imaging workup (Fig 18) (55,56). In this section, we discuss the region- or organ-based imaging approach to the most prevalent irAEs.

Head and Neck

The most prevalent irAEs in the craniocervical region are two endocrine-related toxic effects: thyroiditis and hypophysitis. These endocrine toxic effects are perhaps the most difficult and under- or misdiagnosed irAEs associated with ICI therapy (57). This could be explained partly because they are mostly subclinical or oligosymptomatic and also because they are not clearly graded in the Common Terminology Criteria for Adverse Events, the standard reference for clinicians. However, it is easy to depict these irAEs with whole-body functional PET because the inflammation process of the affected gland increases FDG metabolism (uptake).

Thyroiditis.—Among endocrine-related adverse events, thyroid dysfunction is far more common than the others, with an incidence of 5%–23% (58). Most cases of thyroid dysfunction are asymptomatic; however, the most common clinical manifestation is acute inflammatory painless thyroiditis, which can cause symptoms of hyperthyroidism (eg, tremor, agitation, and palpitation). Regular thyroid laboratory tests allow confirmation of the diagnosis.

At PET/CT, the thyroid gland will demonstrate diffuse FDG uptake (normally, the thy-

roid does not demonstrate any FDG uptake), mostly with normal size at CT (Fig 5) (59). It is not common to see diffuse gland enlargement, and only in rare cases are cervical reactive lymph nodes with FDG uptake observed (Fig 5). Functional imaging can depict thyroid inflammation even before laboratory changes are observed and allows prediction of development of thyroid dysfunction (60).

Most thyroid inflammation is self-limited and does not require steroid therapy; consequently, it tends to disappear at follow-up PET. Normally, there is no need for further imaging workup, as it cannot be mistaken for disease progression.

Hypophysitis.—ICI-induced toxic effects of the hypophysis are uncommon, occurring in 0.5%–7% of patients, more often during anti-CTLA-4 or dual-blockade therapy (58). They are not severe (grade 1 or 2) in most cases and are often oligosymptomatic, but some symptoms may occur, such as fatigue, headache, and visual field changes, which indicate the possibility of such an entity (52). Another way to diagnose pituitary gland toxic effect is when it appears as secondary adrenal insufficiency; in this case, hormonal tests play an important role in diagnosis.

At whole-body PET/CT, diffuse FDG uptake in the hypophysis (which is normally non-FDG avid) can be seen, and the gland can sometimes be enlarged (Fig 19) (36). As it is important to differentiate autoimmune hypophysitis from new metastatic disease, specific and high-resolution imaging is necessary; hence, complementary brain MRI with hypophyseal direct views is needed. In most cases of hypophysitis, the gland is enlarged at MRI and shows diffuse enhancement (57,61). Conversely, metastatic disease would occur as a focal pituitary lesion or a brain metastasis with sellar involvement.

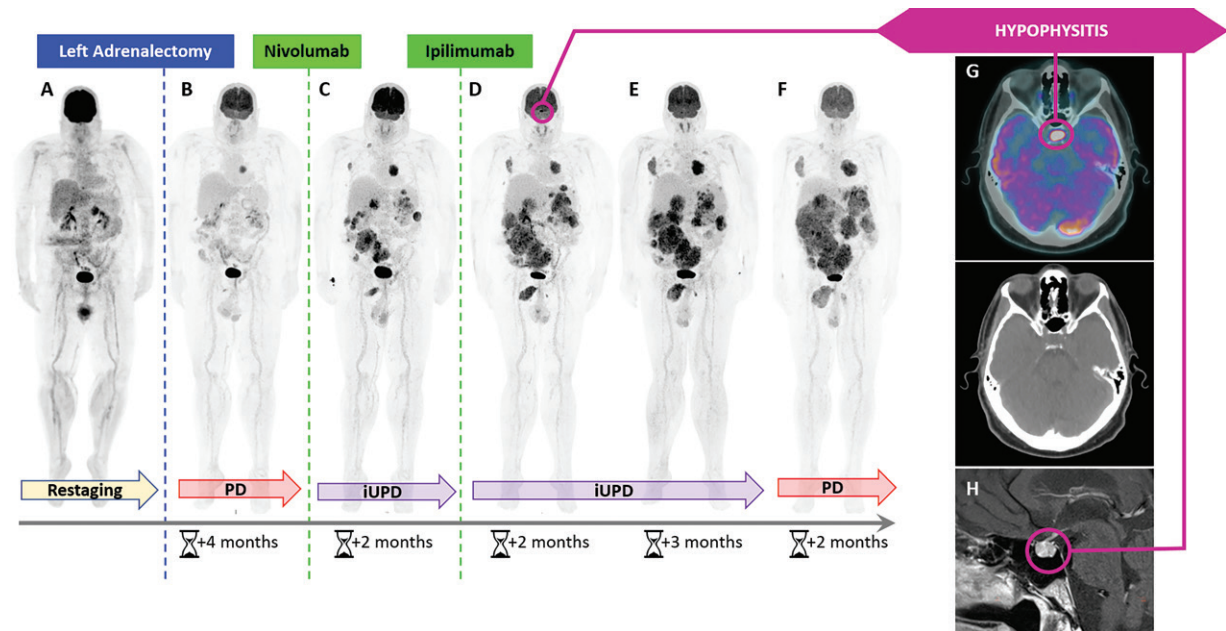


Figure 19. Immunotherapy-related hypophysitis in a 51-year-old man with metastatic melanoma. *A*, MIP FDG PET image shows the appearance at restaging. *B*, Image after left adrenalectomy shows progressive disease (PD). *C*, Image after nivolumab therapy shows immune-unconfirmed progressive disease (iUPD). *D*, *E*, Images after ipilimumab therapy show iUPD. *F*, Follow-up image shows confirmed progressive disease. *G*, Axial FDG PET/CT image shows ipilimumab-induced hypophysitis. *H*, Axial CT (top) and sagittal MR (bottom) images of the hypophysis show an enlarged and diffusely enhanced gland.

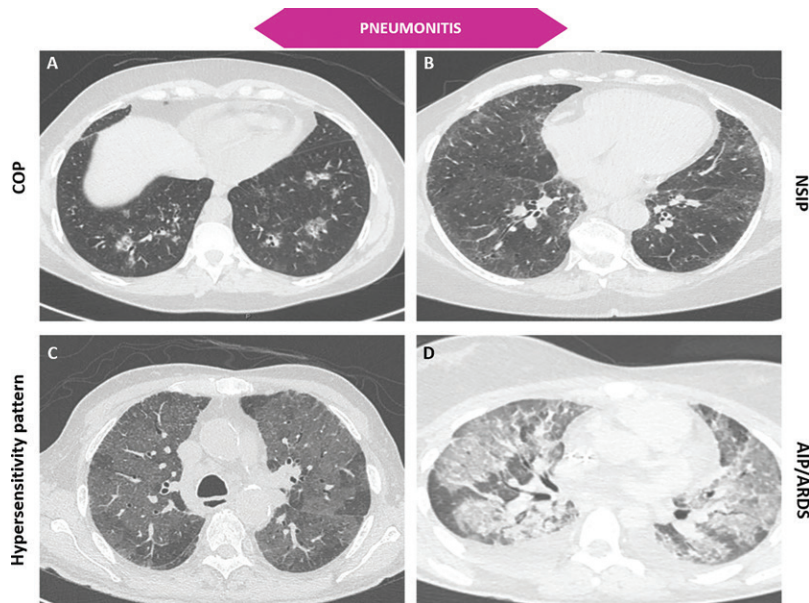


Figure 20. Axial CT images of the four most common patterns of immunotherapy-induced pneumonitis. *A*, Cryptogenic organizing pneumonia (COP) involves multifocal regions of consolidation and ground-glass opacities (GGOs) with a peripheral and basilar distribution. *B*, Nonspecific interstitial pneumonia (NSIP) involves GGOs and reticular opacities with a subpleural distribution. *C*, Hypersensitivity pneumonitis involves multifocal GGOs with a centrilobular distribution and mosaic attenuation. *D*, Acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS) involves diffuse GGOs and traction bronchiectasis.

Thorax

The most common irAE in the thoracic region is lung inflammation (pneumonitis). The incidence is 1%–10%; in contrast to other irAEs, it is more prevalent with anti-PD-1 drugs and with combination therapy (54,57). Pneumonitis is highly variable in onset and severity: one-third of patients are asymptomatic, while the most common symptoms are dyspnea and dry cough; however, fever, chest pain, and hemoptysis are uncommon (54,62). Previous lung radiation

therapy and fibrosis are risk factors for anti-PD-1 pneumonitis.

There are essentially four imaging patterns of pneumonitis at chest CT (63) (Fig 20): (a) cryptogenic organizing pneumonia (COP), which involves multifocal ground-glass opacities (GGOs) and consolidations with a predominantly peripheral distribution; (b) nonspecific interstitial pneumonia (NSIP), which involves mild GGOs with a tendency for peripheral distribution; (c) hypersensitivity pneumonitis (HP), which involves diffuse mild

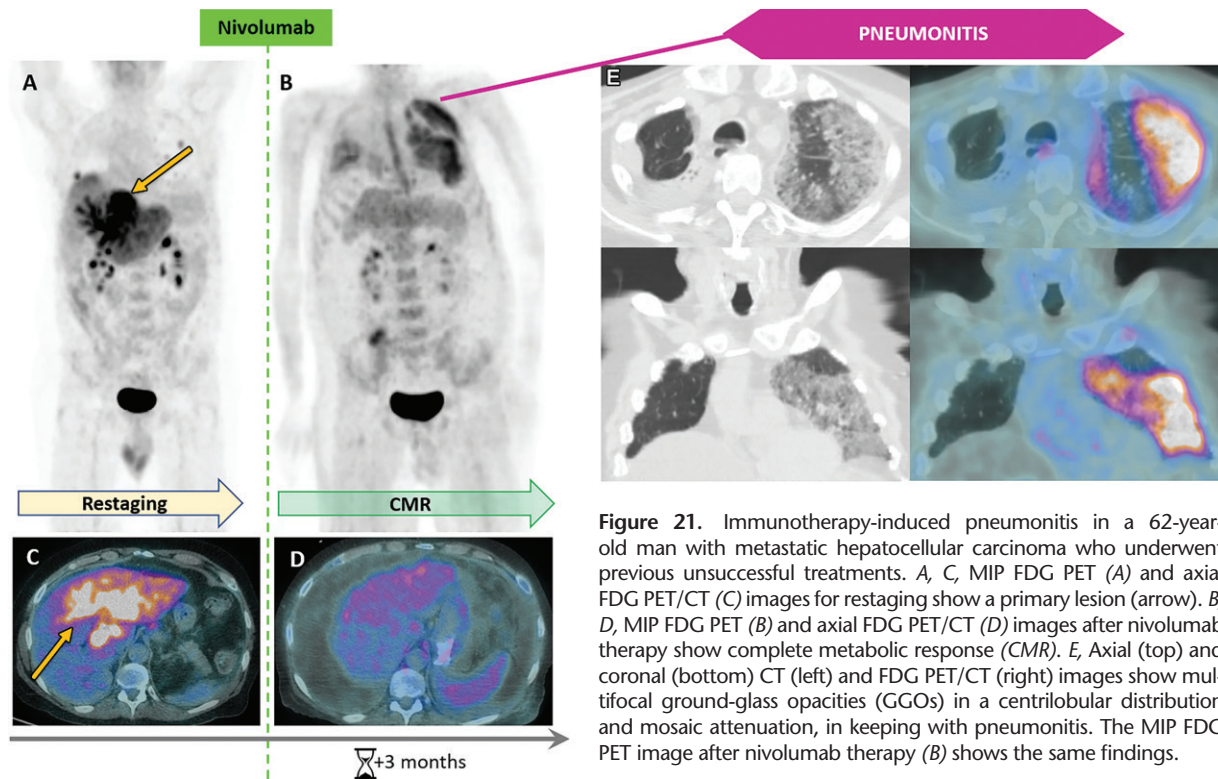


Figure 21. Immunotherapy-induced pneumonitis in a 62-year-old man with metastatic hepatocellular carcinoma who underwent previous unsuccessful treatments. *A*, *C*, MIP FDG PET (*A*) and axial FDG PET/CT (*C*) images for restaging show a primary lesion (arrow). *B*, *D*, MIP FDG PET (*B*) and axial FDG PET/CT (*D*) images after nivolumab therapy show complete metabolic response (CMR). *E*, Axial (top) and coronal (bottom) CT (left) and FDG PET/CT (right) images show multifocal ground-glass opacities (GGOs) in a centrilobular distribution and mosaic attenuation, in keeping with pneumonitis. The MIP FDG PET image after nivolumab therapy (*B*) shows the same findings.

GGOs and centrilobular nodules; and (*d*) acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS), which involves diffuse GGOs, consolidations, and lung volume loss (Fig 21).

COP is the most prevalent pneumonitis pattern, followed by the HP, AIP, and NSIP patterns (64). Moreover, there is a correlation between the radiologic pattern and the clinical severity of pneumonitis. The AIP/ARDS pattern is associated with the most severe toxicity and possibly the worst prognosis, followed by the COP and HP/NSIP patterns (65,66).

At PET/CT, such pulmonary opacities can show different intensities of FDG uptake, depending on the inflammatory infiltration. Patients may also have reactive mediastinal lymphadenopathy and possibly pleural effusions (57). Along with clinical parameters, such imaging patterns can help stratify patients according to severity and guide treatment management.

Many of the symptoms and radiologic findings of pneumonitis overlap with those of infectious pneumonia or, less frequently, with those of tumor progression. Thus, diagnosis can remain somewhat challenging. For afebrile patients, immune-mediated pneumonitis is generally the first differential diagnosis.

Abdomen

Gastrointestinal.—In the abdominal region, the gastrointestinal tract is most commonly affected

by immune-mediated inflammation. Potentially any part of the gastrointestinal tract can be affected. Colitis and diarrhea are the most prevalent abdominal irAEs. These are more strongly associated with combination therapy (up to 50%) or anti-CTLA-4 therapy alone (up to 22%) (52,54,57). Despite often being underreported by patients, colitis is the primary reason why patients undergoing ICI treatment arrive at the emergency department (62). Other symptoms besides diarrhea include abdominal pain, vomiting, fever, and hematochezia.

Imaging is not fundamental in such a scenario because the diagnosis is mainly clinical. However, it can be seen at imaging, despite its suspicion, and clinicians should be promptly warned. The more common imaging findings are diffuse or segmental bowel wall thickening, with increased enhancement and FDG uptake (36) (Fig 22). There are no specific imaging features for immune-related colitis as compared with other inflammatory bowel conditions. Severe cases will probably require discontinuation of ICI therapy, and infectious causes (specifically *Clostridium difficile*) should be ruled out with stool testing (52,54,57).

Hepatitis or Pancreatitis.—Hepatic toxic effects caused by ICI therapy are relatively common (up to 19% of cases) and often asymptomatic. However, patients can present with fatigue, nausea, fever, or jaundice (54,57,62). The diagnosis

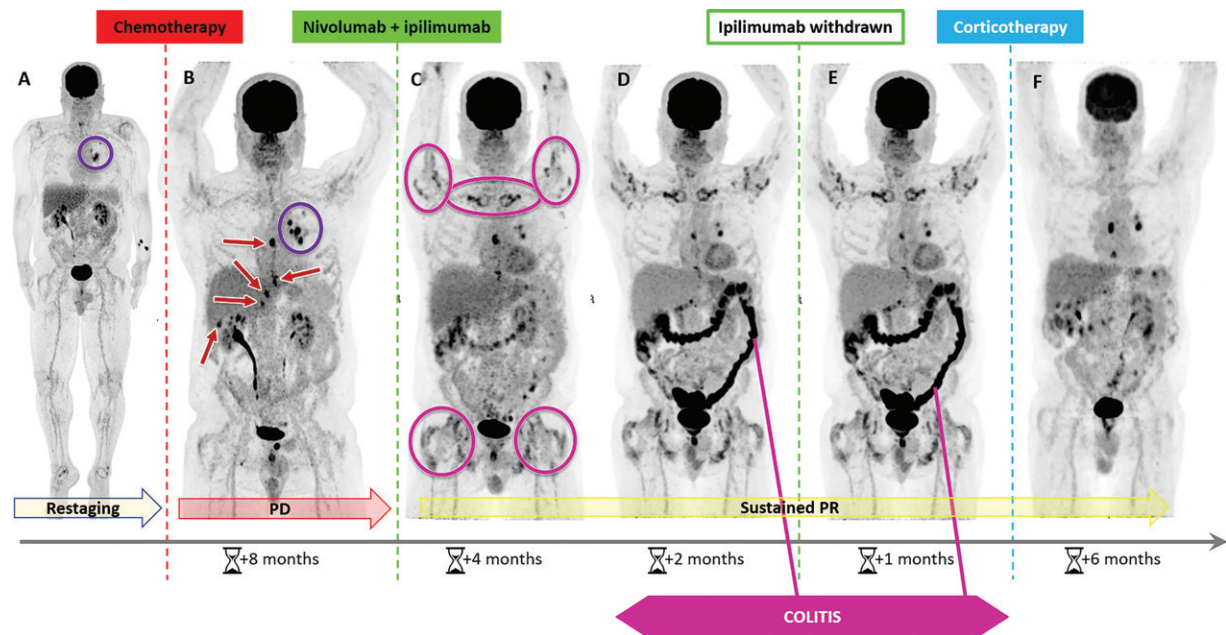


Figure 22. Immunotherapy-induced colitis, arthritis, and synovitis in a 67-year-old man with metastatic non-small cell lung cancer. *A*, MIP FDG PET image shows the appearance at restaging. Purple circle = active mediastinal nodal disease. *B*, Image after chemotherapy shows progressive disease (PD). Purple oval = active mediastinal nodal disease, arrows = PD sites after chemotherapy: thoracic and abdominal nodes. *C*, *D*, Images after nivolumab and ipilimumab therapy show a sustained partial response (PR), with the appearance of multiple sites of arthritis and synovitis (pink ovals) and mild and diffuse bowel hypermetabolism. *E*, Image after withdrawal of ipilimumab therapy shows that the findings have not resolved. *F*, Image shows that the findings responded to steroid therapy.

is mainly clinical, with elevated transaminase level (alanine transaminase [ALT] or aspartate transaminase [AST]) or hyperbilirubinemia. Such a diagnosis can be challenging to distinguish in patients with preexisting liver metastases or underlying hepatic dysfunction. In this context, imaging can play an important role in differentiating between metastatic progression and hepatitis. Imaging findings of liver inflammation can be hepatomegaly, periportal edema, or heterogeneous liver enhancement, with or without diffuse FDG uptake (36,67).

Pancreatitis can also be seen in response to ICI therapy, although with low incidence (up to 4%). While most patients are asymptomatic, typical manifestations include upper abdominal pain, nausea, vomiting, and elevated levels of pancreatic enzymes (amylase and lipase). Imaging is important to rule out metastases. Imaging findings are the same as for non-immune-related pancreatitis, showing diffuse pancreatic enlargement with FDG uptake at PET, with or without peripancreatic fat stranding (36,67) (Fig 23).

Adrenal Dysfunction.—Primary adrenal dysfunction related to ICI therapy is rare and can manifest as primary adrenal insufficiency related to inflammation (adrenalitis). It could also be life threatening owing to the lack of cortisol. Imaging could be important to distinguish this

condition from adrenal metastatic disease, and it can appear as mild and diffuse gland enlargement with FDG uptake at PET/CT (depending on the inflammatory level). Secondary adrenal insufficiency related to hypophyseal toxic effects is the most common ICI-related adrenal dysfunction but may not affect the adrenal glands at imaging.

Musculoskeletal and Rheumatologic Effects

Musculoskeletal symptoms are relatively common during ICI therapy, including arthralgia (up to 43%) and myalgia (up to 21%) (68). Inflammatory musculoskeletal processes are unusual irAEs, with arthritis/tenosynovitis (1%–7%) being more prevalent than myositis/fasciitis (<1%). They may also occur together in specific rheumatologic syndromes (including connective tissue diseases), such as rheumatoid arthritis, polymyalgia rheumatica, lupus erythematosus, and Sjögren syndrome (68–70).

Clinical and imaging manifestations of musculoskeletal inflammatory processes tend to be symmetrical and involve multiple joints (polyarthritis) or tendons/muscles. They can appear as joint effusion, synovial thickening, or tendon/muscle edema with increased enhancement. PET can show increased FDG uptake in these structures (54) (Figs 24, 25).

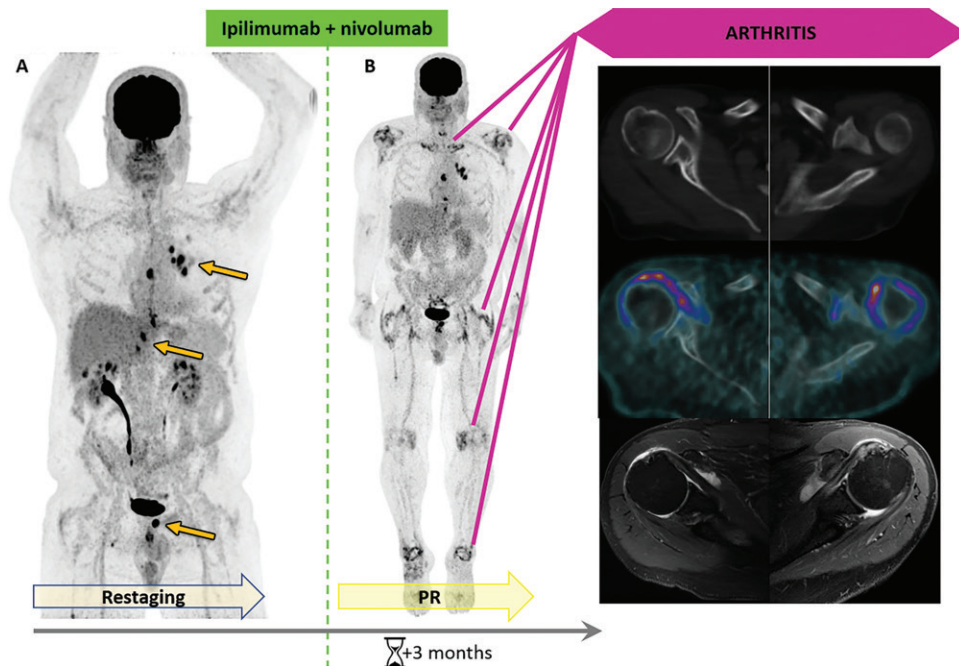
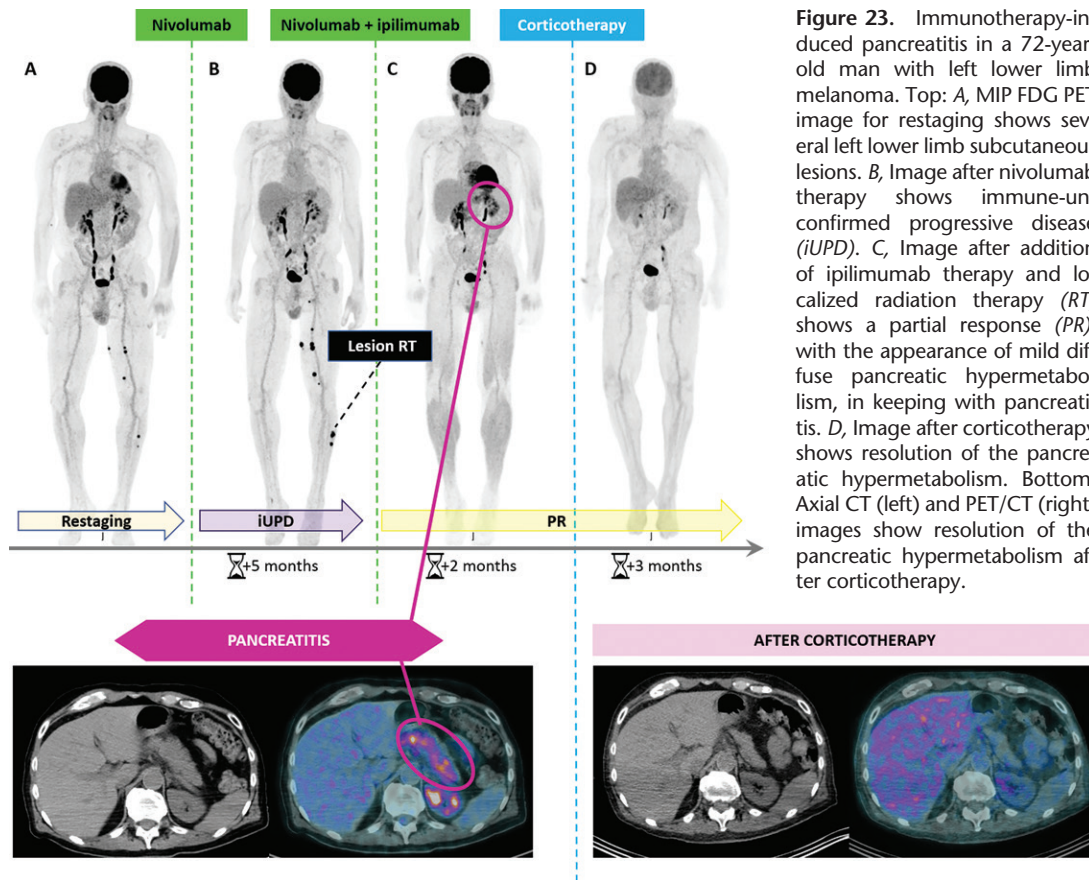


Figure 24. Immunotherapy-induced arthritis in a 60-year-old man with non-small cell lung cancer with neuroendocrine differentiation, previously treated with radiation therapy and chemotherapy. *A*, MIP FDG PET image for restaging shows recurrence of disease, with nodal, hepatic, and bone metastases (arrows). Combined therapy with ipilimumab and nivolumab was started; the patient later presented with polyarthralgia. *B*, Left: Image 3 months later shows a partial response (PR) and onset of bilateral symmetrical hypermetabolism throughout multiple joints. Right: Axial CT (top), PET/CT (center), and T2-weighted MR (bottom) images of the shoulders show articular effusion and capsular FDG uptake, consistent with polyarthritis.

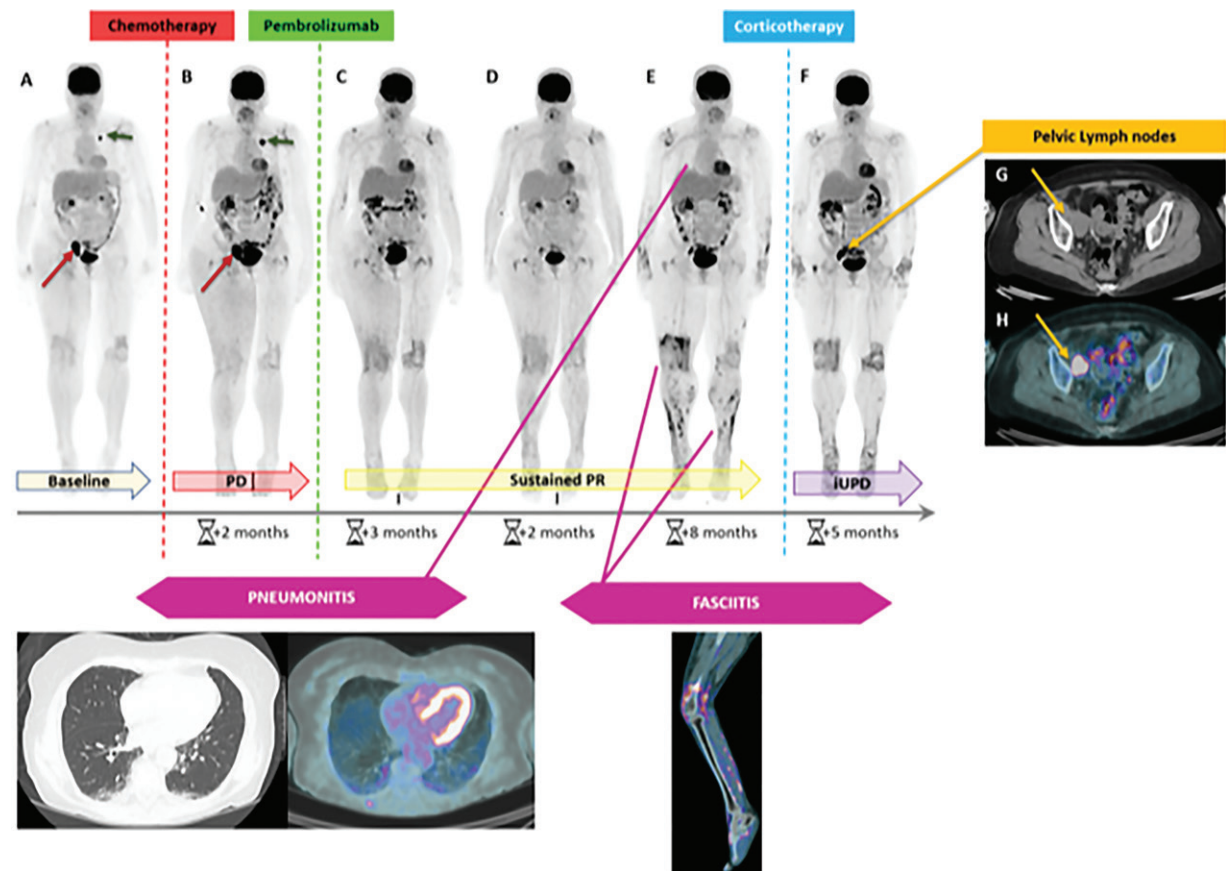


Figure 25. Immunotherapy-induced pneumonitis and fasciitis in a 63-year-old woman with metastatic high-grade sarcoma of the right lower limb. *A*, MIP FDG PET image at diagnosis shows pulmonary (green arrow) and pelvic (red arrow) lesions. *B*, Image after chemotherapy shows progressive disease (PD). Green arrow = pulmonary lesion, red arrow = pelvic lesion. *C–E*, Images after pembrolizumab therapy show a sustained partial response (PR), associated with the appearance of pneumonitis and fasciitis. *F*, Image after steroid therapy shows resolution of the pneumonitis and fasciitis. There is a new pelvic node (arrow), which represents immune-unconfirmed progressive disease (iUPD). *G*, *H*, Axial CT (*G*) and FDG PET/CT (*H*) images show the new pelvic node (arrow).

Miscellaneous or Systemic Effects

Sarcoidosis or Sarcoidlike Reaction.—Sarcoidosis or sarcoidlike reaction is a systemic granulomatous reactive process that is indistinguishable from sarcoidosis and is associated temporally with drug exposure. ICIs can induce a reactive inflammatory process (71). This can occur with any ICI and in different oncologic scenarios, and most patients are asymptomatic (noted with fortuitous imaging findings). Data concerning the incidence during ICI therapy are lacking, but it is estimated to occur in up to 5%–7% of patients (71–73).

The main organs affected by sarcoid granulomatosis are the lungs, lymph nodes, skin, cardiovascular system, and central nervous system. At PET/CT, the most prevalent findings are FDG-avid enlarged lymph nodes, which are usually thoracic (mediastinal and bilateral hilar) but can also be cervical or abdominal (Figs 26, 27). Other imaging features include perilymphatic pulmonary nodules, focal lung consolidation, and less commonly splenic or hepatic nodules (71–73).

Dermatologic Toxic Effects.—Cutaneous irAEs are among the most common side effects of ICI treatment. Some different clinical manifestations can be seen (rash, pruritus, and vitiligo) and are often mild. However, there is no real role for imaging in this context, and these irAEs are rarely seen at PET/CT (52,54,57,74).

Perspectives

FDG PET is evolving with several strengths in assessing response to ICI therapy. However, refinements of PET-based criteria (eg, immunotherapy-modified PERCIST [imPERCIST]) have been tested by some authors. They have been found to improve both the discriminative and prognostic performance of FDG PET as a response biomarker (75). Semiquantitation is one of the marked advantages of PET, allowing objective and reproducible assessment of tumor response. However, since the beginning of its use in clinical practice, semiquantitative PET has focused only on SUV and some of its variations (eg, SUV_{max} , SUV_{mean} , and SUV corrected for lean body mass [SUL]).

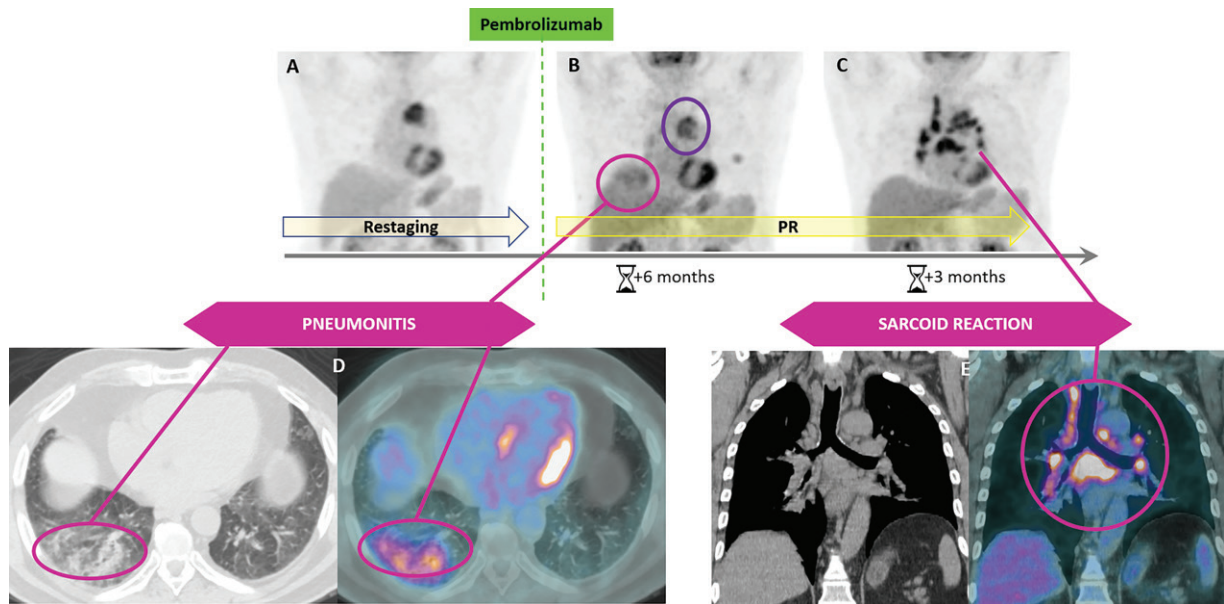


Figure 26. Immunotherapy-related pneumonitis and sarcoid reaction in a 72-year-old man with thymic carcinoma. *A*, FDG PET image for restaging shows the primary lesion. *B*, *C*, Images after pembrolizumab therapy show a partial response (PR) (purple oval), associated with the appearance of mild and diffuse ground-glass opacities (GGOs) in the lower right lung (pink circle) and emergence of enlarged mediastinal nodes with moderate hypermetabolism, suggestive of pneumonitis and sarcoid reaction, respectively. *D*, Axial CT (left) and FDG PET/CT (right) images show the GGOs (pink ovals). *E*, Coronal CT (left) and FDG PET/CT (right) images show the enlarged mediastinal nodes (pink circle).

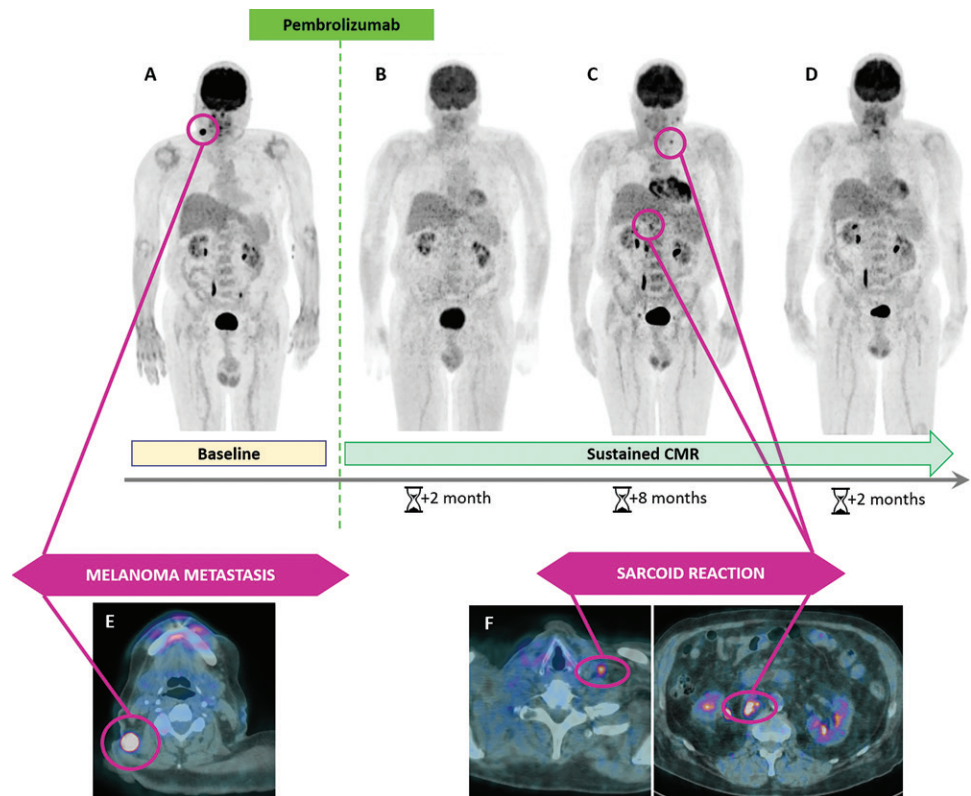


Figure 27. Immunotherapy-related sarcoid reaction mimicking nodal metastases in a 75-year-old man with melanoma of unknown primary origin. *A*, MIP FDG PET image for staging shows right cervical lymphadenopathy (pink circle). *B*, Image after pembrolizumab therapy shows complete metabolic response (CMR). *C*, Follow-up image shows onset of a few cervical, mediastinal, and abdominal hypermetabolic lymph nodes (pink circles). Biopsy of the lymph nodes demonstrated sarcoidlike reaction. *D*, Image from the next follow-up study shows spontaneous resolution of the hypermetabolic lymph nodes. *E*, Axial FDG PET/CT image for staging shows the right cervical lymphadenopathy (pink circle). *F*, Axial FDG PET/CT images show the hypermetabolic lymph nodes (pink ovals).

New semiquantitative parameters—such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG)—have been tested, with encouraging results for different tumors and treatments, including ICI therapy (41). One interesting and recent example is integration of MTV with lesion morphologic volume into a ratio (metabolic-to-morphologic volume ratio [MMVR], represented as a percentage of the division of MTV by the morphologic tumor volume), which appears to have strong predictive power for response to PD-L1 blockade but also for tumor PD-L1 expression in non-small cell lung carcinoma (76). Another emerging and promising approach is determination of whole-body MTV as a tool to assess the total burden of disease, avoiding sampling error and providing a more comprehensive overview of disease extension as well as a better predictive and prognostic biomarker (77,78).

Recently, labeling of immune checkpoint blockers with PET isotopes—such as zirconium 89 and ^{18}F —has opened a promising field for molecular imaging in assessment of ICI therapy (79,80). These techniques are based mainly on labeling antibodies against PD-1 or PD-L1 antigens. Together with other applications, use of labeled antibodies in PET has been termed *immunoPET*. ImmunoPET has the potential to overcome some current inaccuracies in patient selection for ICI therapy by using tissue-based biomarkers related to tissue sampling, as well as allowing prediction and even evaluation of responses. Additionally, in assessing whole-body in vivo expression of immune checkpoint antigens, immunoPET allows visualization of nontumor tracer accumulation, potentially predicting adverse effects arising from this nontarget accumulation.

Last but not least, artificial intelligence and radiomics-based approaches have shown great potential for managing the increasing number of PET-derived parameters (78). Some authors have proposed multiparametric radiomics signatures to combine multiple PET-derived parameters and thereby improve both the predictive and prognostic power of PET-derived biomarkers (81).

Conclusion

Immunotherapy, particularly ICI therapy, has revolutionized oncology practice, changing the natural history of several neoplastic diseases. As a relatively new, expensive, and potentially toxic therapy that is unfortunately not suitable for all patients, ICI therapy requires reliable and effective biomarkers, not only to monitor the therapeutic response but also for patient selection, prediction, and prognosis. Additionally, the unique biologic effects of ICI can give rise to

both misinterpretation of responses and suboptimal diagnosis of adverse events with morphology-based imaging (ie, CT and MRI) and the main imaging criteria (eg, RECIST).

In this challenging scenario, PET appears to be a valuable tool, allowing early and accurate assessment of the four traditional pillars of response in oncology (complete response, partial response, stable disease, and progressive disease). It also allows identification of newly recognized situations, such as pseudoprogression or hyperprogression, as well as many new irAEs.

There are no perfect diagnostic modalities or response criteria, and PET and its derived criteria have some limitations. Thus, morphology-based criteria remain important, are widely available, and are continuously updated and refined. However, early metabolic changes—which are temporally closer to the behavior of the disease—reproducible and semiquantitative assessment of disease activity (including whole-body approaches), the potential for generating predictive or prognostic biomarkers, and high sensitivity for detection of irAEs are advantages of PET. When combined with consolidated morphologic criteria, PET can play an essential role in reliably assessing response to ICI therapy and adverse events during immunotherapy as one of the main treatments for cancer.

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