FDG PET/CT–based Response Assessment in Malignancies

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Response is the logical outcome measure of a treatment in a clinical or research setting. Objective response assessment involves the use of a test to segregate patients who are likely to experience improved survival from those who are not. Early and accurate response assessment is critical for determining therapy effectiveness in clinical settings, for effective trial designs comparing two or more therapies, and for modulating treatment on the basis of response (ie, response-adapted therapy). 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) PET/CT can provide both functional and structural information about a disease process. It has been used at several stages of patient management, including imaging-based tumor response assessment, for various malignancies. FDG PET/CT can be used to differentiate patients with lymphoma who have a residual mass but no residual disease after treatment (ie, complete responders) from those who have a residual mass and residual disease after treatment. Similarly, in solid malignancies, the functional changes in glucose uptake and metabolism precede the structural changes (commonly seen as tumor shrinkage) and necrosis. Response assessment criteria have been developed on the basis of findings on FDG PET/CT images and are continuously being revised to ensure standardization and improve their predictive performance.

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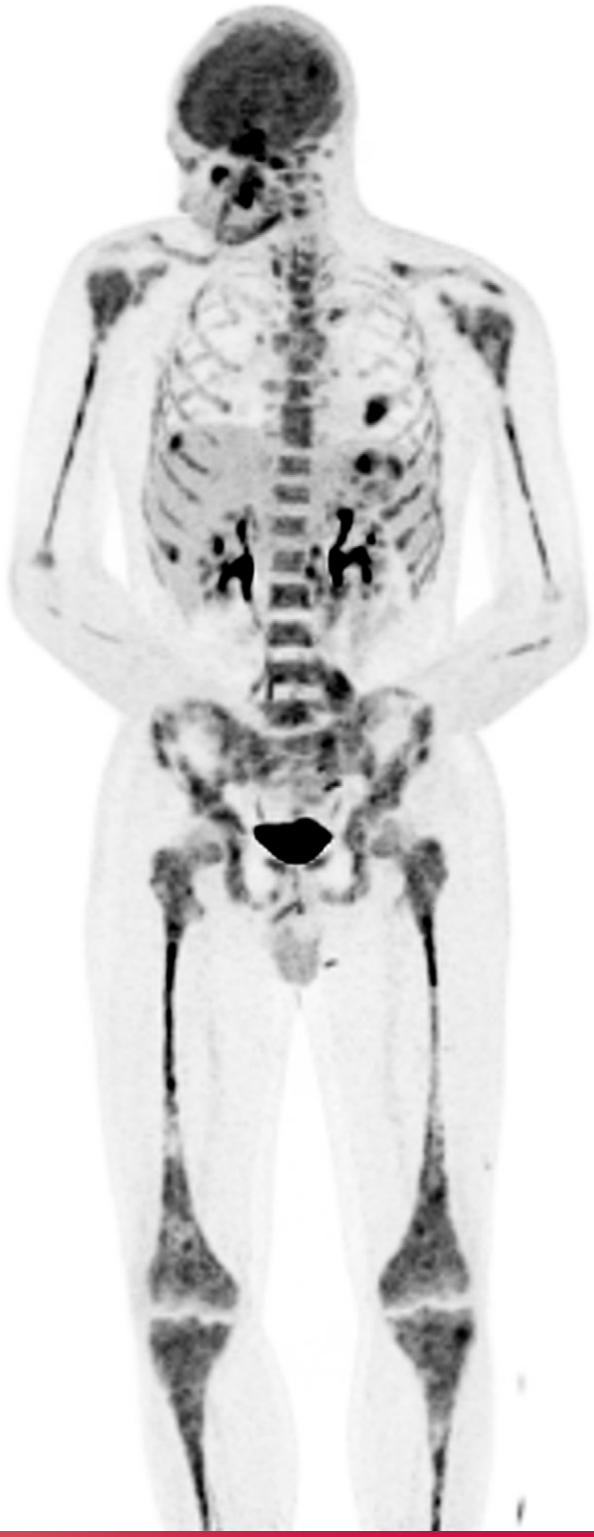

Introduction

Functional imaging with 2-[fluorine 18]fluoro-2-deoxy-D-glucose (FDG) PET/CT has a vital role in the evaluation of several malignancies. FDG is a radioactive analog of glucose and follows the initial steps of glucose transport and phosphorylation. At its core, the intracellular concentration of FDG can be described as a function of its delivery to the cell, its rate of transport through the cell membrane, and the activity of hexokinase and the dephosphorylating enzymes (1). Since most malignant cells demonstrate increased aerobic glycolysis (ie, Warburg effect), FDG is preferentially localized to these tumor cells compared with many normal tissues. Because most metabolic processes are common to various malignancies, FDG and most other radiopharmaceuticals are not specific to a single type of tumor (2,3). Apart from sites of physiologic biodistribution and their variants, FDG avidity is also seen in several nonneoplastic processes (4–8). Indeed, FDG has been used increasingly to detect areas of active infection and inflammation (9–11). This is important to know, as tumor lesions might have residual FDG uptake after treatment owing to inflammatory changes rather than to viable tumor cells. The distinction between FDG uptake due to posttreatment inflammation and that due to viable tumor is not always apparent and can complicate response assessment.

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Abbreviations: CMR = complete metabolic response, CR = complete response, FDG = 2-[fluorine 18]fluoro-2-deoxy-D-glucose, HL = Hodgkin lymphoma, MIP = maximum intensity projection, NHL = non-HL, PD = progressive disease, PERCIST = PET Response Criteria in Solid Tumors, PMD = progressive metabolic disease, PMR = partial metabolic response, PR = partial response, SD = stable disease, SUL = SUV corrected to lean body mass, SUL_{mean} = mean SUL, SUL_{peak} = peak SUL, SUV = standardized uptake value, SUV_{max} = maximum standardized uptake value

TEACHING POINTS

- A favorable treatment response should correspond to a durable clinical benefit to the patient, which includes improvement in survival outcomes (ie, progression-free survival, overall survival), control of local tumor growth and distant spread, prevention of tumor-related adverse effects, and improvement in quality of life. Among these, control of tumor growth is a useful criterion that can be objectively assessed at early time points following the initiation of therapy.
- Response assessment is a continuous spectrum, but for the sake of convenience it is often categorized into distinct groups: CR, PR, SD, and progressive disease (PD). Use of this categorization, irrespective of the tumor type, the tumor's inherent biologic factors, and the related patient-specific prognosis, can lead to an inaccurate estimate of treatment efficacy. For example, achieving sustained SD with symptom control in a patient with advanced non–small cell lung cancer may denote a favorable response with improved survival outcomes, despite it not being categorized as an objective response (CR or PR).
- Certain sites (eg, Waldeyer ring, area of bone marrow activation after colony-stimulating factors) have increased physiologic FDG uptake, which is often higher than that in the normal mediastinum and/or liver. If these sites were involved at initial staging, a CR may be inferred if the posttherapy uptake has normalized and is similar to that in the surrounding normal tissue, even if it is higher than that in the mediastinum and/or liver.
- Increased FDG uptake in a single lymph node and/or the appearance of any new FDG-avid foci compatible with lymphoma is sufficient to denote PD, even if the other disease sites are responding favorably. The key words here are *compatible with lymphoma;* hence, caution must be exercised when interpreting lymph nodes that might otherwise represent infection or inflammation or marrow FDG uptake due to activation from colony-stimulating factors or systemic inflammation.
- PERCIST 1.0 does not require the same lesion to be measured at the baseline and follow-up PET studies. Rather, the hottest lesion on each study is measured.

FDG PET/CT may be used at several time points during the evaluation of a malignancy. Succinctly, applications for FDG PET/CT during this evaluation include initial evaluation of a lesion when its origin (especially neoplastic or nonneoplastic) is uncertain, guiding to the most representative and accessible site for histopathologic sampling, initial staging of a known malignancy to determine the disease extent and disease activity for treatment planning, monitoring response to treatment, and surveillance in cases of high-risk malignancies and to evaluate suspected disease recurrence (12–17). In this article, we elaborate on the role of FDG PET/CT for assessing response to treatment in FDG-avid lymphoid and solid malignancies.

Assessment of Treatment Response in Malignancies

Clinical Response to Treatment

Tumor response to treatment in the strict sense includes any change in the tumor and its microenvironment resulting from the effects of a particular therapy. Therefore, the tumor response can be favorable (to the patient) or unfavorable, although the word *response* traditionally has been used in oncology to refer to a favorable outcome and the word *progression* has been used to denote an unfavorable outcome. A favorable treatment response should correspond to a durable clinical benefit to the patient, which includes improvement in survival outcomes (ie, progression-free survival, overall survival), control of local tumor growth and distant spread, prevention of tumor-related adverse effects, and improvement in quality of life. Among these, control of tumor growth is a useful criterion that can be objectively assessed at early time points following the initiation of therapy.

Objective Measurements of Response to Treatment

Historically, treating physicians have used quantitative measurements to understand how a patient is responding to treatment. Initially, these techniques were crude and included physical palpation and use of a ruler to obtain rough estimates of the tumor size before and after therapy. However, a major limitation with this method was low reproducibility. A pivotal study (18) showed that these measurements have significant intrareader and interreader variability and suggested using a cutoff of a greater than 50% reduction in the tumor cross-sectional area to denote objective response, which would limit the measurement error–related objective response rate to less than 10%. Gradually, the techniques shifted from physical palpation of the tumors to measuring their dimensions on radiographs or CT images, but the basic fundamental approach of relying on tumor size as a surrogate for treatment response remained the same (19).

Limitations of Anatomic Size–based Criteria for Treatment Response Assessment

In addition to the previously stated problem with reproducibility, solely using changes in tumor size to assess treatment response has other challenges. First, tumors might have lesions that are nonmeasurable at imaging, such as malignant ascites, pleural effusion, and sclerotic bone metastases (20). Since these lesions cannot be "measured" and compared by using the conventional methods, the accuracy of response assessment may be limited, especially in patients in whom these lesions predominate the overall disease burden.

Second, not all tumors respond to treatment similarly. For example, a change in the pattern of internal enhancement is one of the early and key signatures of response in gastrointestinal stromal tumors (21). During the early posttreatment period, these tumors may have loss of internal enhancement and a homogeneous hypoattenuating appearance at CT, without a significant change in size. Therefore, while these tumors are responding favorably to treatment, the size criteria for response at anatomic imaging might not always be met.

Table 1: Deauville Five-Point Scale for FDG PET–based Assessment of HL and NHL

Score	Interpretation (Based on FDG Uptake)
1	Lesion uptake similar to or lower than background tissue uptake
2	Lesion uptake ≤ mediastinal blood pool uptake
3	Lesion uptake > mediastinal blood pool uptake but ≤ liver uptake
4	Lesion uptake moderately higher than liver uptake
5	Markedly increased lesion uptake* and/or new sites of disease

Note.—NHL = non-HL.
*Suggested as uptake two to three times higher than the SUV_{max} in the normal liver.

Similarly, with Hodgkin lymphoma (HL), a residual "mass" is often seen at the end of treatment in patients with a complete response (CR). This is a result of the inflammatory process culminating in fibrosis and does not represent viable tumor (22). However, if only the tumor size were assessed at anatomic imaging, those patients with disease in remission would be classified as having either a partial response (PR) or stable disease (SD).

Third, assessing response only on the basis of tumor size ignores other significant parameters, such as tumor growth rates. A rapidly growing tumor that shows partial shrinkage following treatment may have worse survival outcomes compared with those of a slow-growing tumor with no shrinkage after treatment (23).

Fourth, measurement of tumor size is a valid option for assessing response to cytotoxic chemotherapies and external-beam radiation. The mechanisms of different targeted agents and immunotherapies are variable, and the tumor shrinkage measurement might not be the most reflective marker of therapy efficacy in these cases (24).

Advantages of Metabolic Imaging–based Criteria for Treatment Response Assessment

FDG PET/CT offers several advantages in response assessment. The changes in glucose metabolism often precede any structural changes in tumor size, enabling an earlier assessment of response (25). Earlier response assessment or the prediction of responder versus nonresponder can help in adjusting further therapy cycles, referred to as response-adapted therapy (26). Assessment of glucose metabolism can be used to differentiate a mass composed largely of viable tumor cells from a fibrotic mass, as in HL (27). FDG PET/CT also provides semiquantitative data in the form of the standardized uptake value (SUV), which denotes the relative uptake of FDG in each region of interest and is an indirect measure of the local glucose metabolism. Measurement of the SUV (typically, the maximum SUV [SUV_{max}]) in a standardized and consistent imaging environment serves as a reproducible parameter that can be assessed and compared between baseline and posttreatment imaging in addition to the visual interpretation (28).

Further Considerations for Treatment Response Assessment

Response assessment is a continuous spectrum, but for the sake of convenience it is often categorized into distinct groups: CR, PR, SD, and progressive disease (PD). Use of this categorization, irrespective of the tumor type, the tumor's inherent biologic factors, and the related patient-specific prognosis, can lead to an inaccurate estimate of treatment efficacy. For example, achieving sustained SD with symptom control in a patient with advanced non–small cell lung cancer may denote a favorable response with improved survival outcomes, despite it not being categorized as an objective response (CR or PR) (23).

In addition, the timing of the response assessment is important. Response can be assessed after treatment completion, when a CR is typically associated with a more favorable outcome than is a PR or nonfavorable response. Earlier response assessment, after one or a few cycles of therapy, may show a minimal change in tumor size but can potentially identify those patients whose tumors are responding poorly versus those whose tumors are responding favorably. This permits early treatment changes, including instituting alternative therapies, treatment intensification in less-than-ideal responders, or de-intensification in patients with an exceptionally good response.

In the next sections, we describe FDG PET–based response assessment in lymphoid malignancies with use of Deauville scores (Table 1), with which tracer uptake in the lesion is compared with that in the mediastinum and liver. The score is then incorporated into the Lugano criteria and used with other parameters to assign one of four responses: CR, PR, SD, or PD (Table 2). We describe the importance of the timing of the response assessment and how interim PET can be used to assess the prognosis and help in early monitoring of response.

Next, we describe response assessment in solid malignancies, emphasizing the PET Response Criteria in Solid Tumors (PERCIST) and how these require strict study conditions (Table 3) to ensure the accuracy of the quantitative measurements used. The measurements of metabolic activity and the differences in these measurements from baseline to follow-up can then be translated into the similar four metabolic response categories (Table 4). Finally, we discuss the unique imaging features and response patterns seen with immune-targeting agents—notably pseudoprogression, hyperprogression, and dissociated response. We recognize that several of the response evaluation criteria described herein have more utility in research studies than in routine clinical practice. However, since the foundation of objective response assessments remains the same, the principles behind these criteria can be used in clinical practice, albeit with limitations in accuracy and generalizability.

Response Assessment in Lymphoid Malignancies

Historic Overview

The first recommendations for response assessment in non-HL (NHL) were made by the International Working Group in 1999 and formed the International Workshop Criteria (IWC) (29). FDG PET findings were added to the original IWC in 2005 to

Table 2: Lugano Classification of Tumor Response with Use of FDG PET/CT

Classification of Response	PET/CT Findings
CR	Deauville score of 1–3 with no new lesions, no bone marrow involvement
PR	Deauville score of 4 or 5 with reduced FDG uptake from baseline, residual bone marrow FDG uptake reduced from baseline, no new lesions
SD	Deauville score of 4 or 5 with no change in FDG uptake from baseline, no change in bone marrow involvement, no new lesions
PD	Deauville score of 4 or 5 with increased FDG uptake from baseline, new or recurrent lesions compatible with lymphoma, or appearance of bone marrow involvement based on increased FDG avidity

Table 3: Requirements for Performing Response Assessment by Using PERCIST

Parameter	Requirements
Timing of baseline PET/CT	Within 3 weeks of starting therapy
Fasting before FDG injection	Fasting for at least 4–6 hours, with serum glucose level of <200 mg/dL before FDG injection
FDG uptake period	Scan should be obtained 50–70 minutes after FDG injection. At follow-up, the uptake period should be within ±15 minutes of the baseline (but >50 minutes).
Injected FDG activity	At follow-up, activity should be within ±20% of the activity injected at baseline
Lesion measurability (only at baseline)	Lesion $SUL_{peak} \geq$ [(1.5 times liver SUL_{mean}) + 2 standard deviations of noise] *Or* if aortic VOI used: lesion $SUL_{peak} \geq$ [(two times aortic SUL_{mean}) + 2 standard deviations of noise]
Comparability of background uptake	Baseline and follow-up scans are comparable if liver SUL_{mean} is 20% of the larger of the two SULs (baseline, follow-up), and the absolute difference in SULs is ≤ 0.3. The same cutoffs apply if the liver was diseased and the aortic blood pool SUL_{mean} was obtained at baseline and follow-up.
Scanner, acquisition protocol, reconstruction software	Use same scanner, acquisition, reconstruction software, and protocol at baseline and follow-up

Note.—SUL = SUV corrected to lean body mass, SUL_{mean} = mean SUL, SUL_{peak} = peak SUL, VOI = volume of interest.

Table 4: Categorical PERCIST-based Response Assessment

Classification of Response	PET/CT Findings (Simplified)
CMR	Complete resolution of FDG uptake within measurable target lesion, disappearance of all other lesions, no new lesions
PMR	≥30% reduction in SUL_{peak}, and absolute SUL_{peak} decline of 0.8 unit between the most FDG-avid lesion at baseline and follow-up. In addition, there should be no identifiable >30% increase in size in the target lesion, no >30% increase in size or SUL_{peak} in the nontarget lesions, and no new lesions compatible with malignancy.
SMD	Not CMR, PMR, or PMD
PMD	≥30% increase in SUL_{peak}, and absolute SUL_{peak} increase of 0.8 unit, or appearance of new lesions

Note.—CMR = complete metabolic response, PMD = progressive metabolic disease, PMR = partial metabolic response, SMD = stable metabolic disease.

form the IWC+PET criteria. FDG PET findings were visually interpreted as positive (any nonphysiologic, increased, focal or diffuse uptake) or negative. A negative PET scan would lead to designating CR (per IWC+PET criteria) in patients previously designated as having CR, unconfirmed CR, PR, SD, or even PD by using the IWC. However, according to the IWC, in patients with PD, the lesion detected at CT must be greater than or equal to 1.5 cm in diameter (≥1 cm for lung lesion) to reliably interpret the PET findings as negative. Lesions smaller than this would be affected by the limited spatial resolution of PET, and the "visually negative" PET scan would not be sufficient to designate CR in these patients with PD according to the IWC.

The IWC+PET criteria, as compared with the IWC alone, enabled better prediction of progression-free survival in patients with NHL (30). FDG PET was included in the 2007 International Harmonization Project (IHP) criteria for assessing response in HL and NHL (31,32), which recommended visual interpretation of the PET images and comparison of the lesion avidity with the mediastinal blood pool avidity to determine response. The interpretation of PET images was

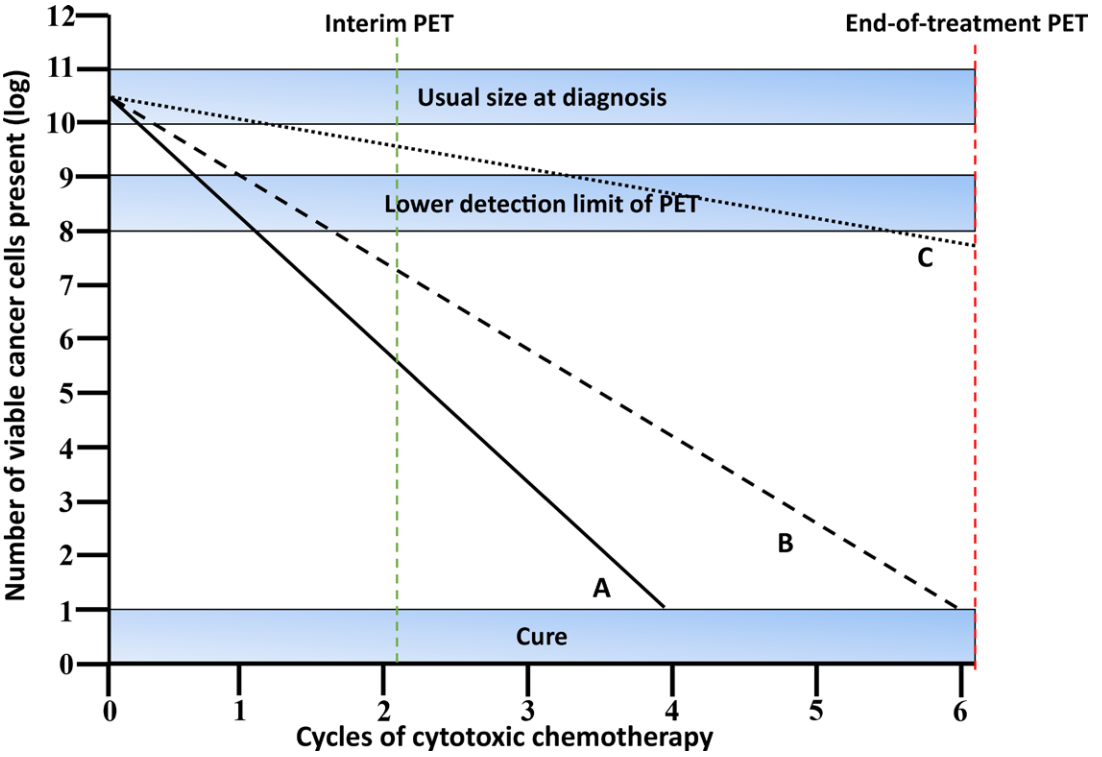


Figure 1. Role of interim PET in assessing treatment response. Three hypothetical curves indicating different cell-killing rates show that three tumors are negative at end-of-treatment PET (red dashed line), but cure is achieved in tumors A and B only. The negative PET-based status of tumor C at the end of treatment is only because the number of tumor cells is below the detectability threshold of current PET technology. Conversely, interim PET performed after two cycles of therapy (green dashed line) can be used to distinguish tumors A and B from tumor C, as tumor C remains positive at PET, while tumors A and B are negative. PET performed early during the treatment course is able to capture both the response and the rate of that response, which is of prognostic significance. (Adapted and reprinted, with permission, from reference 36.)

similar to that performed with use of the IWC+PET criteria, with a few caveats. Tracer uptake in large masses (≥2 cm) had to exceed that in the mediastinal blood pool to be classified as positive for lymphoma. However, for smaller (<2 cm) lesions, the uptake had to exceed that in the surrounding background tissue to be classified as positive. Similar provisions were made for lung nodules and splenic and liver lesions. Furthermore, a waiting period for performing PET after chemotherapy (at least 3 weeks, ideally 6–8 weeks) and radiation therapy (~8–12 weeks) was recommended to minimize the false-positive PET results due to therapy-induced inflammation.

At an international workshop organized in Deauville, France, in 2009, an innovative FDG PET–based scoring system was proposed for response assessment in both HL and NHL. With this system, commonly referred to as the Deauville five-point scale (Deauville scoring), a visual interpretation of FDG PET findings with the lesion avidity compared with the avidity of the mediastinal blood pool and liver (Table 1) was proposed (33). The Deauville criteria were a shift from the traditional criteria, with which percentage changes in SUV were used, and instead involved a simple method of assessing images in both clinical and research settings. The Deauville score was initially developed to perform interim response assessment and complement IHP-based end-of-treatment response assessment. The Deauville score provided more flexibility in interpreting varying degrees of tracer uptake seen on interim PET images with use of a five-point scale, compared with the binary (positive or negative) classification used in the IHP criteria. Further clarifications were made to the Deauville criteria. These clarifications included validation of the criteria for use in cases of HL and NHL at interim and end-of-treatment time points (27,34).

The Lugano classification introduced in 2014 further expanded on the use of Deauville scores for response assessment (35). Notably, a Deauville score of 4 was suggested to represent uptake of more than the SUV_{max} in a large region of the normal liver, and a score of 5 was to be assigned to uptake two to three times higher than the SUV_{max} in the normal liver. In addition, the assessment of response at sites with high physiologic FDG uptake was further clarified (described later in this section).

Timing of Response Assessment

Interim imaging is performed during the treatment course to segregate *responders,* defined as those who are likely to benefit from therapy continuation, from *nonresponders,* defined as those who are unlikely to benefit from continuing the same therapy. This early assessment provides prognostic information and can help avoid unnecessary treatment in patients who are not likely to respond favorably. In addition, it can help in instituting an alternate management plan in patients who are not likely to benefit from continuing the same treatment (26). Figure 1 (36) demonstrates the value of performing interim PET. In patients with HL, the findings of interim PET performed after two cycles of chemotherapy have been found to be the most representative of long-term outcomes compared with the findings of PET performed after one or four cycles (37). The prognostic value of interim PET has been higher in patients with HL than in those with NHL (37) and higher in patients with aggressive, as compared with indolent, disease (38).

Assessing Response at FDG PET/CT by Using Deauville Scores and Lugano Classification

The Lugano classification is aimed at improving the evaluation of patients with lymphoma and minimizing ambiguity—at staging, for assessing response, and during follow-up. This

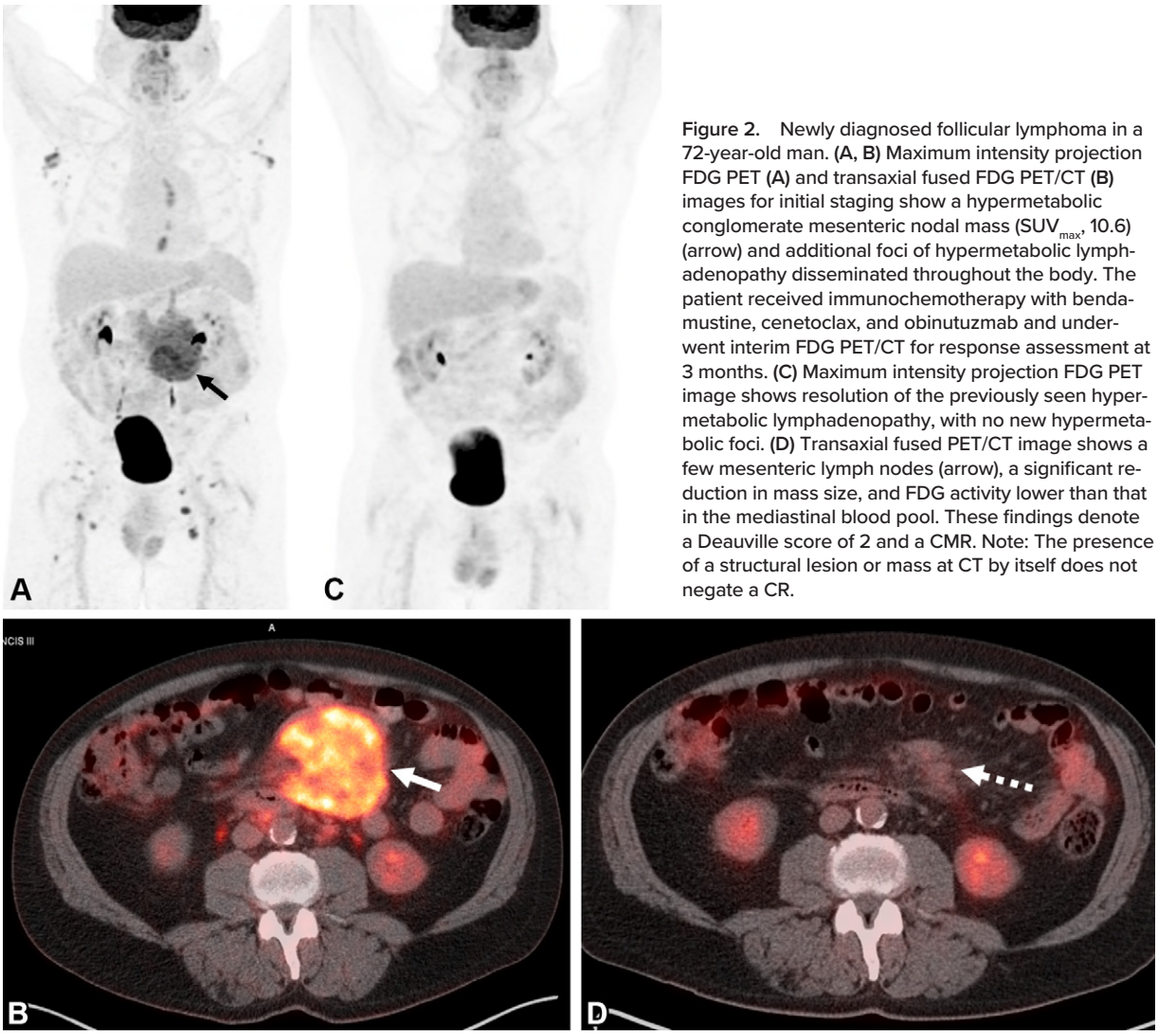


Figure 2. Newly diagnosed follicular lymphoma in a 72-year-old man. **(A, B)** Maximum intensity projection FDG PET **(A)** and transaxial fused FDG PET/CT **(B)** images for initial staging show a hypermetabolic conglomerate mesenteric nodal mass (SUV_{max}, 10.6) (arrow) and additional foci of hypermetabolic lymphadenopathy disseminated throughout the body. The patient received immunochemotherapy with bendamustine, cenetoclax, and obinutuzmab and underwent interim FDG PET/CT for response assessment at 3 months. **(C)** Maximum intensity projection FDG PET image shows resolution of the previously seen hypermetabolic lymphadenopathy, with no new hypermetabolic foci. **(D)** Transaxial fused PET/CT image shows a few mesenteric lymph nodes (arrow), a significant reduction in mass size, and FDG activity lower than that in the mediastinal blood pool. These findings denote a Deauville score of 2 and a CMR. Note: The presence of a structural lesion or mass at CT by itself does not negate a CR.

classification includes a recommendation for FDG PET/CT as the standard for assessing FDG-avid lymphomas (the majority of lymphomas) and CT assessment for non–FDG-avid lymphomas (some small lymphocytic lymphoma or chronic lymphocytic leukemia, mycosis fungoides, and marginal zone lymphoma) and in cases in which PET/CT is not available (35). The Lugano classification is based on the interpretation of PET/CT findings with use of Deauville scores and is used to assign one of the four traditional response categories (CR, PR, SD or PD [Table 2]) to a scan. The Deauville score–based interpretation of FDG PET/CT findings and subsequent categorization based on the Lugano criteria are discussed in the following sections.

Complete Response.—CR denotes a Deauville score of 1 or 2 with no new lesions and no bone marrow involvement at interim or end-of-treatment FDG PET/CT. The presence of a residual mass at CT does not negate a CR (Fig 2). A Deauville score of 3 also indicates a CR with standard treatment; however, the definition of this score in a trial setting varies according to the timing of assessment, trial objectives (eg, de-escalation of therapy in response-adapted trials), and clinical context (35). For example, a Deauville score of 3 may be interpreted as an inadequate response to prevent the undertreatment of patients in a trial exploring therapy de-escalation in complete responders. An additional caveat is that certain sites (eg, Waldeyer ring, area of bone marrow activation after colony-stimulating factors) have increased physiologic FDG uptake, which is often higher than that in the normal mediastinum and/or liver. If these sites were involved at initial staging, a CR may be inferred if the posttherapy uptake has normalized and is similar to that in the surrounding normal tissue, even if it is higher than that in the mediastinum and/or liver (Fig 3).

Partial Response.—PR denotes a Deauville score of 4 or 5 at interim PET, with reduced FDG uptake in the lesions and/or bone marrow compared with the uptake at baseline, regardless of a residual mass or masses, and no new lesions. These findings, when seen on interim PET/CT images, indicate responding disease but denote residual disease when they are seen at end-of-treatment PET (Fig 4).

Stable Disease.—SD denotes a Deauville score of 4 or 5 with no significant change in FDG uptake in the lesions and/or bone marrow from the baseline at interim or end-of-treatment PET

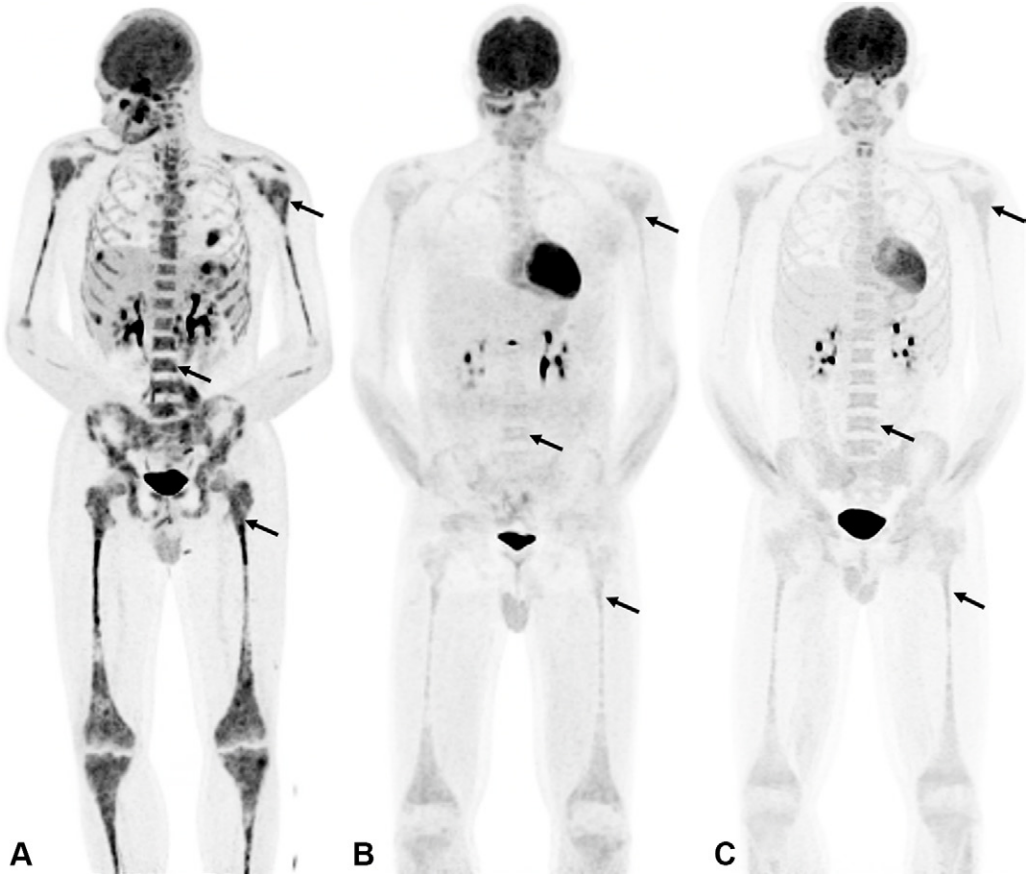


Figure 3. High-grade B-cell lymphoma seen on maximum intensity projection (MIP) FDG PET images in a 16-year-old adolescent boy. Only skeletal lesions are shown. **(A)** Initial staging image shows nodal involvement above and below the diaphragm, in addition to involvement of the liver, paranasal sinuses, paraspinal soft tissue, pleura, and bone marrow in the axial and appendicular skeleton (arrows); other, nonskeletal lesions are not shown on this image. The patient was enrolled in a clinical trial and started on a combined immunochemotherapy with myeloid colony–stimulating factor. **(B)** Interim image at 2 months shows interval resolution of nodal and extranodal disease (Deauville score, 1). Mild diffuse FDG uptake (arrows) is noted in the bone marrow, with substantial reduction in uptake compared with the uptake at initial scanning. Although the activity in the marrow is similar to or slightly higher than that in the liver, it likely represents physiologic marrow activity due to activation from the colony-stimulating factors. **(C)** Findings (arrows) on end-of-treatment image at 7 months confirm continued complete treatment response.

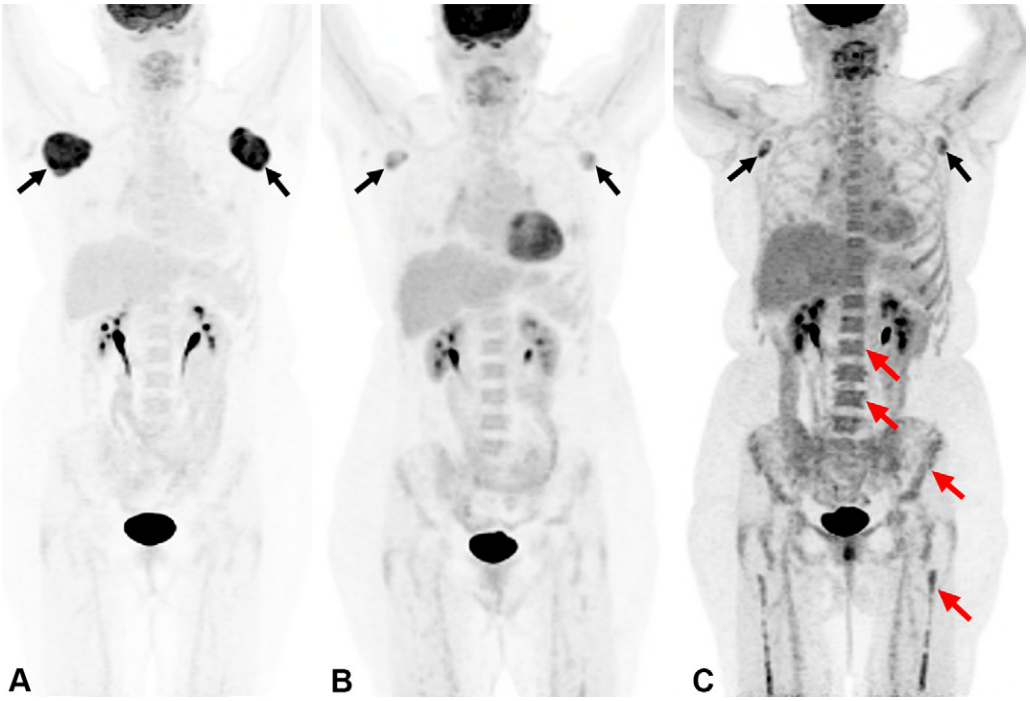


Figure 4. Diffuse large B-cell lymphoma on MIP FDG PET images in a 68-year-old woman. **(A)** Initial staging image shows increased FDG uptake in bilateral axillary nodal masses (arrows) (left-side SUV_{max}, 34.5). The patient received two cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and pegfilgrastim (a granulocyte colony–stimulating factor). **(B)** Interim image 2 months after the baseline study shows the bilateral axillary nodal masses (arrows) with reduced size and FDG uptake (left-side SUV_{max}, 4.9). Activity is moderately higher than that in the liver, denoting a Deauville score of 4. These findings are consistent with PR. The patient completed four cycles of R-CHOP and pegfilgrastim. **(C)** End-of-treatment image 2 months after the interim study shows persistent FDG uptake in the bilateral axillary nodal masses (black arrows) (left-side SUV_{max}, 5.4), with no significant changes from the interim study (Deauville score, 4). This was interpreted as residual disease. Note the diffusely increased FDG uptake in the bone marrow (red arrows) due to pegfilgrastim-induced marrow activation, which is more pronounced at end-of-treatment PET.

and no new lesions. SD translates to no response to therapy—neither a favorable response nor disease progression (Fig 5).

Progressive Disease.—PD denotes a Deauville score of 4 or 5 with an increase in FDG uptake in preexisting lesions and/or an appearance of new FDG-avid foci compatible with lymphoma at interim or end-of-treatment PET (Fig 6). The increase in uptake is assessed visually and leads to a higher score (from 4 at interim to 5 at end of treatment) or is noted as a marked increase in uptake when the interim score was

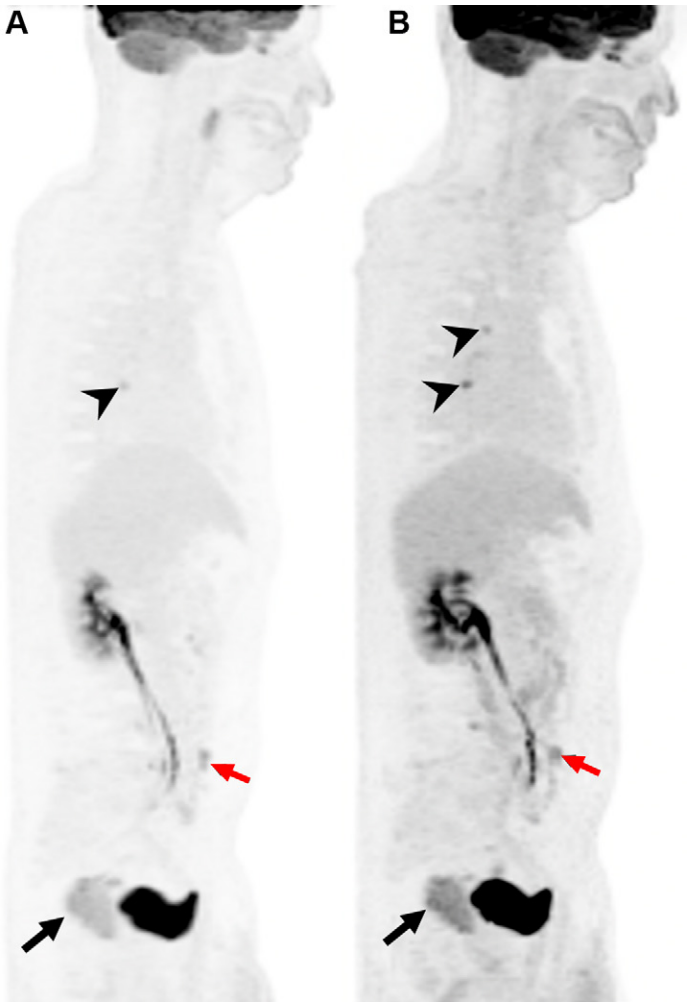


Figure 5. Transformed diffuse large B-cell lymphoma in the setting of underlying follicular lymphoma seen after immunochemotherapy in a 62-year-old man. **(A)** Right sagittal MIP FDG PET image for evaluation of suspected recurrence shows increased FDG uptake in a perirectal soft-tissue mass (black arrow) (SUV_{max}, 8) and in omental (red arrow) and mesenteric soft-tissue masses. The patient received obinutuzumab and bendamustine, and FDG PET/CT was performed for reassessment 2 months after the previous study. **(B)** Right sagittal MIP FDG PET image for response assessment shows persistent FDG activity in the perirectal mass (black arrow) (SUV_{max}, 6.8) and in the omental (red arrow) and mesenteric soft-tissue masses, with no significant change. These findings denote a Deauville score of 4 with SD. Note the FDG-avid foci in the thorax (arrowheads), representing reactive hilar and mediastinal lymph nodes.

5 (highest possible score). Special emphasis must be placed on assessing the lymphomatous involvement of the spleen, which may manifest solely as increased FDG uptake (higher than that of liver) with or without focal lesions, and/or as an increase in size. Increased FDG uptake in a single lymph node and/or the appearance of any new FDG-avid foci compatible with lymphoma is sufficient to denote PD, even if the other disease sites are responding favorably. The key words here are *compatible with lymphoma;* hence, caution must be exercised when interpreting lymph nodes that might otherwise represent infection or inflammation (Fig 5) or marrow FDG uptake due to activation from colony-stimulating factors or systemic inflammation (Fig 4).

Quantification of Response at FDG PET/CT

The Lugano classification assigns response categories based on visual assessment according to Deauville scores. It does not directly capture the quantitative information from the baseline and follow-up scans, which might be more accurate than visual interpretation alone. The change in SUV (ΔSUV) quantifies the change in metabolic activity and can be calculated as follows:

$$\Delta SUV = \Delta SUV_{max}\% \times [(SUV_{fol} - SUV_{bas})/SUV_{bas}],$$

where $\Delta SUV_{max}\%$ is the percentage change in SUV_{max}, and SUV_{fol} and SUV_{bas} are the SUVs at follow-up and baseline, respectively. The baseline and follow-up measurements of SUV_{max} are performed for the hottest lesion (disease-compatible lesion with the highest SUV_{max}) at each time point, which might not necessarily be the same lesion. Use of the ΔSUV improves interobserver agreement (in terms of percentage differences in SUV_{max} from baseline to follow-up versus visual scoring using Deauville scores) and reduces any ambiguity that is associated with visual assessment (39,40). Studies (38,39,41) have shown that the ΔSUV with a cutoff of a greater than 66% decline from baseline to midtreatment may be a better predictor of response compared with Deauville-based assessment. However, the data are still insufficient to permit large-scale clinical implementation.

Response Assessment in Solid Malignancies

In 1999, the European Organization for Research and Treatment of Cancer (EORTC) released its guidelines on standardization of FDG PET and provided a framework for PET-based response assessment (42). The EORTC criteria were based on the percentage change in tumor SUVs and the extent of FDG uptake. Although not explicitly indicated, the EORTC criteria were primarily directed toward solid tumors, according to the majority of studies that were reviewed for its formulation. The PERCIST were introduced by Wahl and colleagues (43) in 2009 with the aim of improving response assessment by using FDG PET/CT.

Applying PERCIST

PERCIST version 1.0 involves the use of SUL (SUV normalized to lean body mass) measurements of the hottest 1-cm^3 volume of tumor at baseline and follow-up to determine response. The peak SUL (SUL_{peak}, in a spherical 1-cm^3 volume of interest) is different from the more widely used SUV_{max}, which is the maximum SUV of a single pixel, corrected for body weight. SUL measurements are more consistent than SUV measurements (normalized to body weight) across variations in body mass, which are not uncommon in patients undergoing chemotherapy. Furthermore, the SUL_{peak} is subject to less variability than the single-pixel SUV_{max}, which is more susceptible to noise (43). PERCIST 1.0 guidelines represent a set of criteria to ensure standardized techniques for response assessment and to confirm the comparability of SUL measurements at baseline and follow-up studies (Table 3). A 3-cm–diameter spherical volume of interest in the right lobe of the normal liver is used for calculation of the background activity in terms of the mean SUL (SUL_{mean}) and its standard deviation

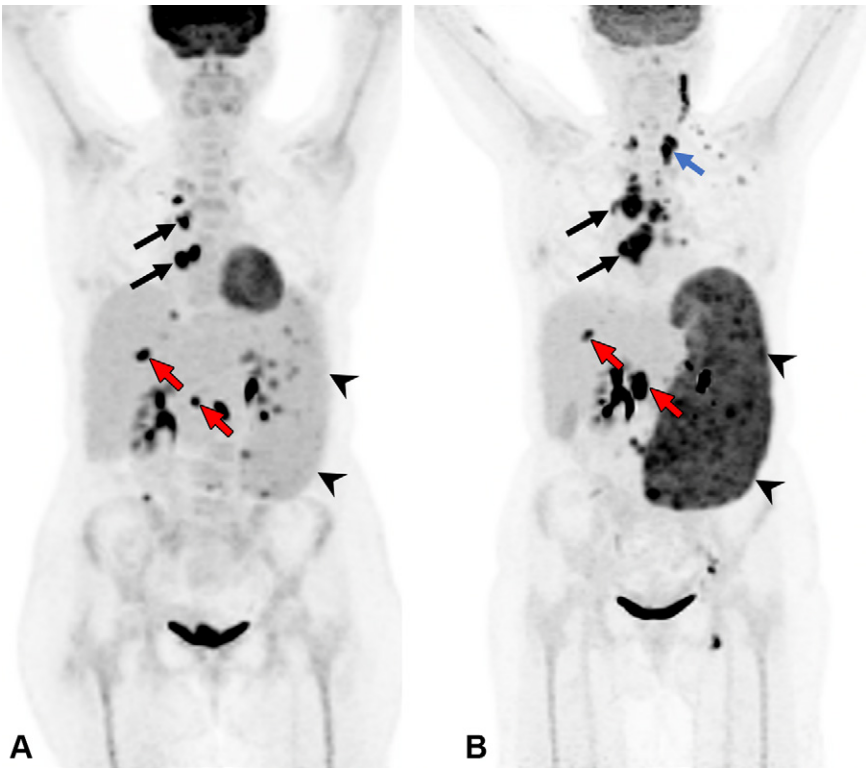


Figure 6. Peripheral T-cell lymphoma in a 57-year-old woman after immunochemotherapy. **(A)** Restaging MIP FDG PET image shows increased FDG uptake in multiple thoracic (black arrows) and abdominal (red arrows) lymph nodes and diffuse increased uptake in an enlarged spleen (arrowheads), with a few focal lesions. The patient received two cycles of romidepsin (a histone deacetylase inhibitor). **(B)** MIP FDG PET image 2 months after the previous study shows multiple new FDG-avid lymph nodes in the cervical and supraclavicular region (blue arrow), axilla, retroperitoneum, and pelvis. In addition, increases in the size and FDG avidity of the previously seen lymph nodes (black and red arrows) and spleen (arrowheads) and new focal lesions are seen. The lesions show markedly increased FDG uptake compared with the liver, denoting a Deauville score of 5 and PD.

(Fig 7). If the liver is involved with the disease process and a background volume of interest cannot be placed reliably, then the descending thoracic aorta may be used. This approach is used to determine whether there is sufficient FDG uptake for measurability in the target lesion on the same scan, as well as to ensure comparability between scans.

The tumor SUL_{peak} at baseline must be 1.5 times the SUL_{mean} of the normal liver (plus 2 standard deviations of noise) to be "assessable" at baseline. PERCIST 1.0 requires measurement of the SUL_{peak} of the single hottest representative lesion for assessing response, although up to five lesions can be measured (maximum of two per organ). Measurement of lesion size, although recommended, is not required for assessing response with use of PERCIST 1.0.

A waiting period of 10 days after chemotherapy and 8–12 weeks after radiation therapy is recommended before performing follow-up PET/CT. This permits resolution of most of the treatment-related flare-inflammatory changes that may otherwise affect response assessment. SUL measurements of the liver and target lesion, similar to the measurements performed at baseline, are recorded at follow-up (Fig 7). Notably, PERCIST 1.0 does not require the same lesion to be measured at the baseline and follow-up PET studies. Rather, the hottest lesion on each study is measured.

Tumor response based on PERCIST 1.0 is a continuous and time-dependent variable, although the traditional response categories have also been used for simplicity and ease of communication (Table 4). The response should be recorded as the percentage change in SUL_{peak} of the target lesion with the time duration (in weeks) in which this response was observed, and the number of new lesions (if any) at follow-up (eg, complete metabolic response [CMR] of 95% at 4 weeks).

Complete Metabolic Response.—For a CMR, the target lesion must show complete resolution of metabolic activity—that is, the FDG uptake in the lesion should be less than the SUL_{mean} of the liver and similar to the adjacent background activity. The FDG uptake in all of the other lesions also should return to background levels, and no new FDG-avid lesions typical of a malignant process should appear. Note that for a CMR, the lesion SUL_{peak} does not have to be reduced to 0. If the FDG-avid lesion at baseline imaging is not visible at follow-up, then the SUL_{peak} of the approximate anatomic location may be recorded (Fig 8).

Partial Metabolic Response.—An SUL_{peak} decline of 30% or greater with an absolute reduction of at least 0.8 SUL unit between the most FDG-avid lesion at baseline and the most FDG-avid lesion at follow-up is required for a partial metabolic response (PMR). Also, there must be no identifiable increase in size of greater than 30% in the target lesion, no increase in size or SUL_{peak} of greater than 30% in the nontarget lesions, and no new lesions compatible with malignancy (Fig 9). The requirement of a 30% or greater decline in SUL_{peak} for PMR in the PERCIST 1.0 is notably more stringent than the 15%–25% decline in SUV required in the EORTC guidelines, and use of the latter requirement is likely to result in an overestimation of PMR according to the current data (43). It is rare for a favorably responding lesion with decreasing FDG uptake to increase in size. Therefore, routine measurement of tumor size is not required in the PERCIST 1.0. It should be performed when an increase in lesion size is apparent on the follow-up study with declining FDG avidity.

Stable Metabolic Disease.—An SUL_{peak} change (increase or decrease) of less than 30% between the baseline and follow-up

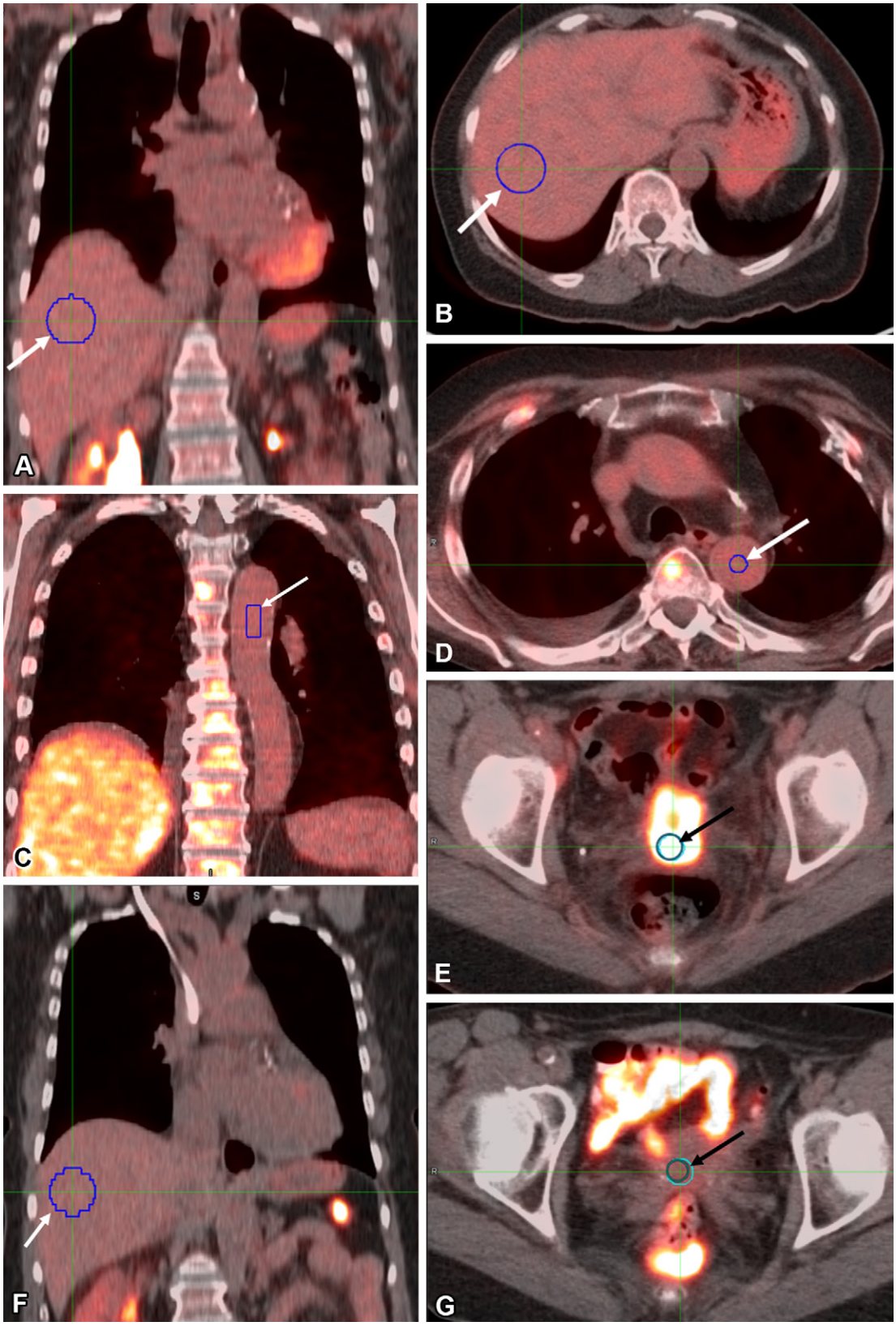


Figure 7. Applying PERCIST based on fused FDG PET/CT findings. **(A, B)** Baseline coronal **(A)** and transaxial **(B)** images show a spherical volume of interest (VOI) (arrow) 3 cm in diameter placed in the right liver lobe, midway between the dome and the inferior margin and excluding areas of high FDG activity, such as the central bile ducts and vessels. The VOI was used to measure the SUL_{mean} and its standard deviation. **(C, D)** Coronal **(C)** and transaxial **(D)** images in a patient with a diseased liver (involving a malignant process) show diffusely increased FDG uptake in the liver that precludes placing a VOI in the liver to estimate background FDG activity. In such cases, a cylindric VOI 1 cm in diameter and 2 cm in length may be placed centrally in the ascending aorta (arrow), with care taken to avoid the vessel wall. **(E)** Transaxial image shows a VOI 1.2 cm in diameter (volume, ~1 mL) placed on a cervical lesion (arrow) and used to measure the SUL_{peak}. **(F)** Coronal follow-up image shows a spherical VOI 3 cm in diameter placed on the right liver lobe (arrow), similar to the VOI placed at baseline imaging, and used to measure the SUL_{mean} and its standard deviation. **(G)** Transaxial image shows a VOI 1.2 cm in diameter (volume, ~1 mL) placed in the lesion (seen in **E**) or in an approximate region of the lesion (arrow) if it has completely resolved, and used to measure the SUL_{peak}.

studies that cannot be categorized as CMR, PMR, or progressive metabolic disease (PMD) is classified as stable metabolic disease (Fig 10). This category is expected to be seen increasingly with use of several of the novel targeted therapies aimed at disease control rather than objective CMR or PMR.

Progressive Metabolic Disease.—An increase in SUL_{peak} of 30% or greater and an absolute increase of at least 0.8 SUL unit in the target lesion, or the development of a new lesion or lesions compatible with the malignancy is categorized as PMD. A 30% or greater increase in size of the target lesion or

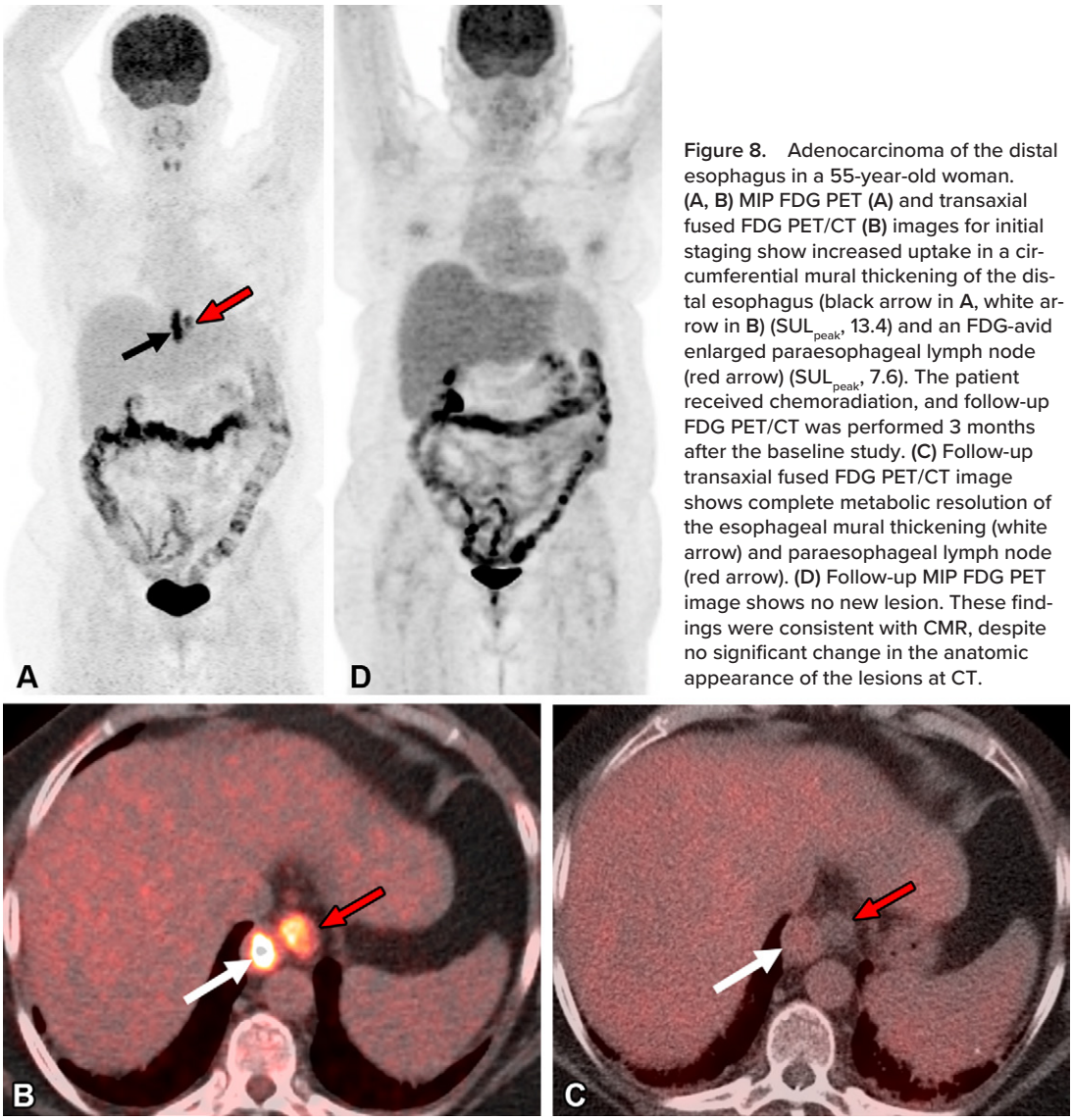


Figure 8. Adenocarcinoma of the distal esophagus in a 55-year-old woman. **(A, B)** MIP FDG PET **(A)** and transaxial fused FDG PET/CT **(B)** images for initial staging show increased uptake in a circumferential mural thickening of the distal esophagus (black arrow in **A**, white arrow in **B**) (SUL_{peak}, 13.4) and an FDG-avid enlarged paraesophageal lymph node (red arrow) (SUL_{peak}, 7.6). The patient received chemoradiation, and follow-up FDG PET/CT was performed 3 months after the baseline study. **(C)** Follow-up transaxial fused FDG PET/CT image shows complete metabolic resolution of the esophageal mural thickening (white arrow) and paraesophageal lymph node (red arrow). **(D)** Follow-up MIP FDG PET image shows no new lesion. These findings were consistent with CMR, despite no significant change in the anatomic appearance of the lesions at CT.

unequivocal progression in the nontarget lesions also is required for this response category.

Response Assessment with Immunotherapy

Immunotherapy involves the use of agents that manipulate the components of the immune system to cause an anticancer effect. Broadly, this includes immunomodulators, cell transplants, antibodies, modified viruses, and cancer vaccines (44). Immune checkpoint inhibitors commonly target cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). Anti–CTLA-4 agents (eg, pilimumab) enhance the antitumoral activity of effector T cells and suppress the activity of regulatory T cells, thereby attenuating the immunosuppressive tumor microenvironment. Anti–PD-1 (eg, nivolumab, pembrolizumab) and anti–programmed cell death ligand 1 (anti–PD-L1) (eg, atezolizumab, avelumab, durvalumab) agents promote the activation and proliferation of T cells, the production of memory T cells, and the binding of T cells with the tumor antigens (44).

Immune checkpoint inhibitors differ from conventional therapy in that they activate the immune system, which then mounts an antitumor response (Fig 11). This leads to distinct patterns of response on conventional and FDG PET/CT images. Briefly, this includes durable responses, even after cessation of therapy (Fig 12); favorable response after an initial period of apparent progression, termed *pseudoprogression;* rapid progression in a clinically deteriorating patient, termed *hyperprogression;* and dissociated responses, with some lesions responding favorably and others progressing with therapy (45). Some of these response patterns, notably durable response and dissociated or mixed response, are also seen with conventional cytotoxic and targeted therapies. In addition, the systemic immune activation with immune checkpoint inhibitors leads to collateral targeting of the normal tissue, which produces undesirable effects. These adverse effects, termed *immune-related adverse events,* often produce unique imaging findings and can be detected on FDG PET/CT images (46,47).

One of the major barriers to accurate response assessment with immunotherapies is the definition of *progression.* Several immune-specific response criteria have been developed, mainly by modifying the existing response criteria to account

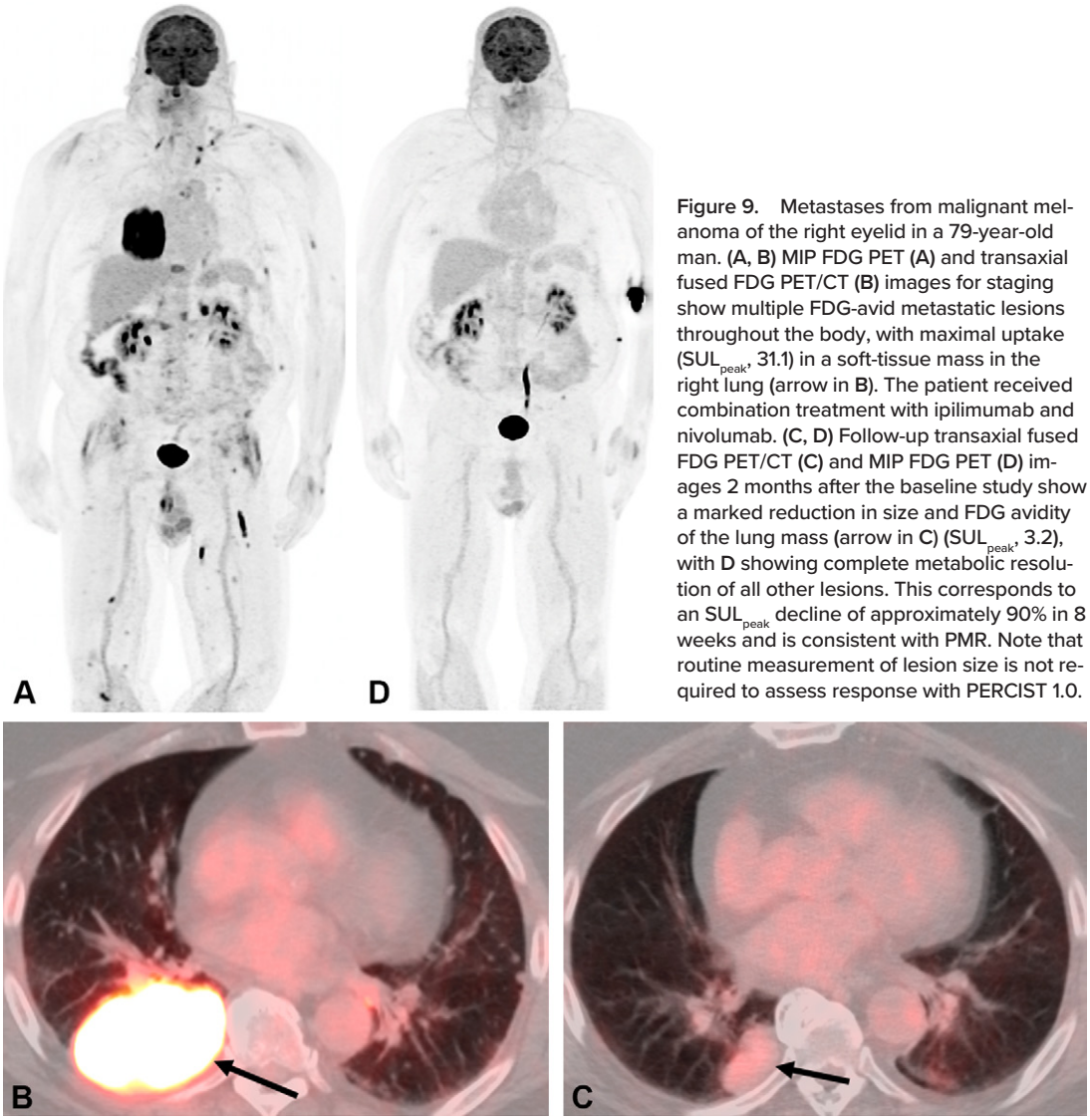


Figure 9. Metastases from malignant melanoma of the right eyelid in a 79-year-old man. **(A, B)** MIP FDG PET **(A)** and transaxial fused FDG PET/CT **(B)** images for staging show multiple FDG-avid metastatic lesions throughout the body, with maximal uptake (SUL_{peak}, 31.1) in a soft-tissue mass in the right lung (arrow in **B**). The patient received combination treatment with ipilimumab and nivolumab. **(C, D)** Follow-up transaxial fused FDG PET/CT **(C)** and MIP FDG PET **(D)** images 2 months after the baseline study show a marked reduction in size and FDG avidity of the lung mass (arrow in **C**) (SUL_{peak}, 3.2), with **D** showing complete metabolic resolution of all other lesions. This corresponds to an SUL_{peak} decline of approximately 90% in 8 weeks and is consistent with PMR. Note that routine measurement of lesion size is not required to assess response with PERCIST 1.0.

for the distinct response patterns with immune-targeting therapies, especially pseudoprogression (48–50). As an example, with the immune PERCIST (adapted from PERCIST and immune-modified RECIST [Response Evaluation Criteria in Solid Tumors]) developed for patients with non–small cell lung cancer, patients with PMD (per PERCIST) are categorized as having unconfirmed PMD, adding a provision for a second FDG PET/CT study at 4–8 weeks to differentiate between pseudoprogression and true progression and permitting continuation of treatment until the progression has been confirmed (50). However, there presently is no consensus on the use of one of these criteria over the others, and further validation in larger cohorts can help translate these criteria into clinical practice. Next, we briefly discuss some of the distinct response patterns seen with immunotherapies.

Pseudoprogression

An initial increase in size or FDG avidity of the preexisting lesions or the appearance of new lesions, often with symptomatic improvement in a patient with a subsequent reduction in tumor burden, denotes pseudoprogression (Fig 13). Pseudoprogression appears to be uncommon, with an incidence of 2%–10% with combination therapies (anti–CTLA-4, anti–PD-1 or anti–PD-L1); hence, most cases with progression at scanning are likely to represent true progression (45,48). Reassessment FDG PET/CT performed at least 4 weeks later can confirm pseudoprogression or true progression. Continued use of immune checkpoint inhibitors is beneficial in patients with pseudoprogression, especially if their clinical course appears to be stable or improving.

Hyperprogression

A rapid increase in lesion size, FDG avidity of the preexisting lesions, and/or (frequently) the appearance of multiple new lesions in a clinically deteriorating patient indicates hyperprogression (Fig 14). Hyperprogression is reported in 4%–29% of patients taking immune checkpoint inhibitors and requires immediate cessation of these agents and a switch to alternate therapies (45). Multiple criteria have been used to define hyperprogression, including a time to treatment failure of less than 2 months, a greater than 50% increase in tumor burden, and a greater than twofold increase in the pace of progression

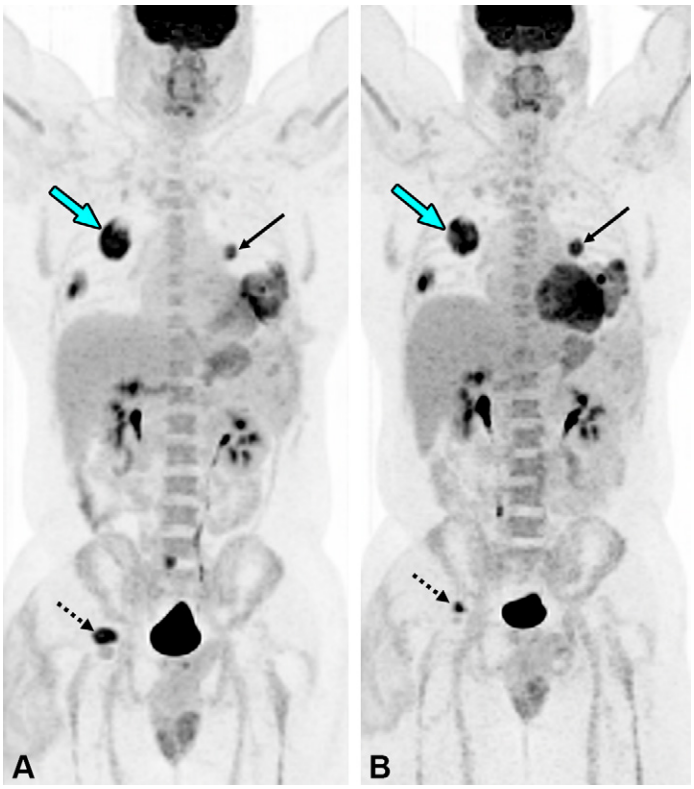


Figure 10. Synovial sarcoma of the right hip, seen after excision of the primary tumor and chemoradiation, in a 47-year-old man. **(A)** MIP FDG PET image for restaging shows hypermetabolic metastatic nodules in both lungs (blue and black solid arrows), with the larger right lung nodule (blue arrow) having the greatest FDG avidity, as well as a metastatic right inguinal lymph node (dashed arrow). **(B)** MIP FDG PET image 2 months later, after completion of chemotherapy, shows disease with no significant interval change. While there is a mild reduction in size and FDG avidity of the right inguinal lymph node (dashed arrow), no significant change is noted in the overall disease, including the largest and most avid lesion in the right lung (blue arrow) and the other lung nodules (solid black arrow). These findings are consistent with stable metabolic disease.

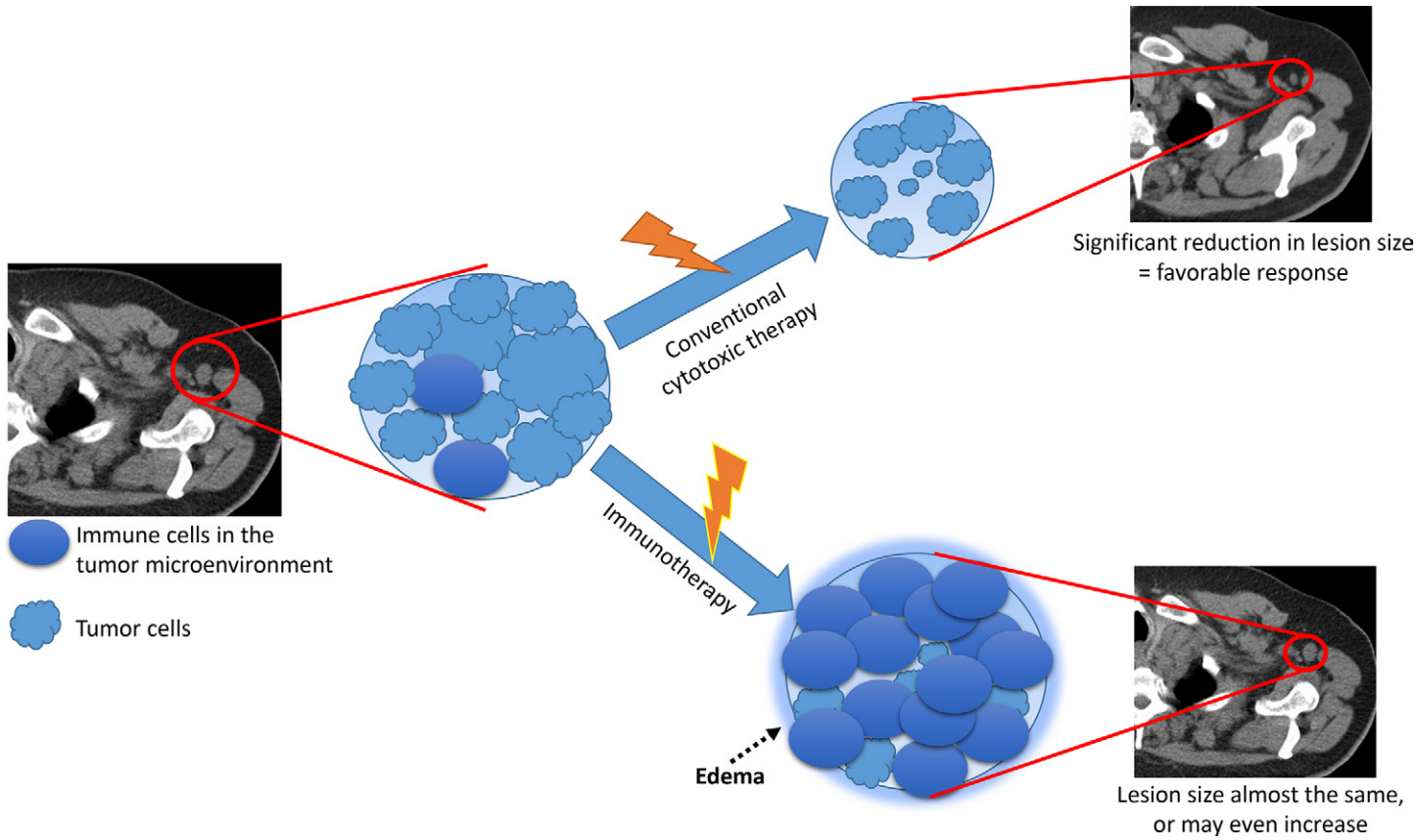


Figure 11. The tumor microenvironment includes tumor cells and immune cells in addition to other components. Conventional cytotoxic therapy acts by means of direct cell killing, leading to a reduction in the number of cells. This is visible as a shrinkage of the tumor at conventional imaging (eg, CT) and translates to a favorable response to therapy. Conversely, immunotherapy (eg, with immune checkpoint inhibitors) leads to recruitment, activation, and proliferation of immune cells. The activated immune response with inflammation alters the composition of the tumor microenvironment, but it cannot be readily identified on conventional images. Thus, grossly, the tumor size appears to be stable or even increased, leading to misclassification as PD.

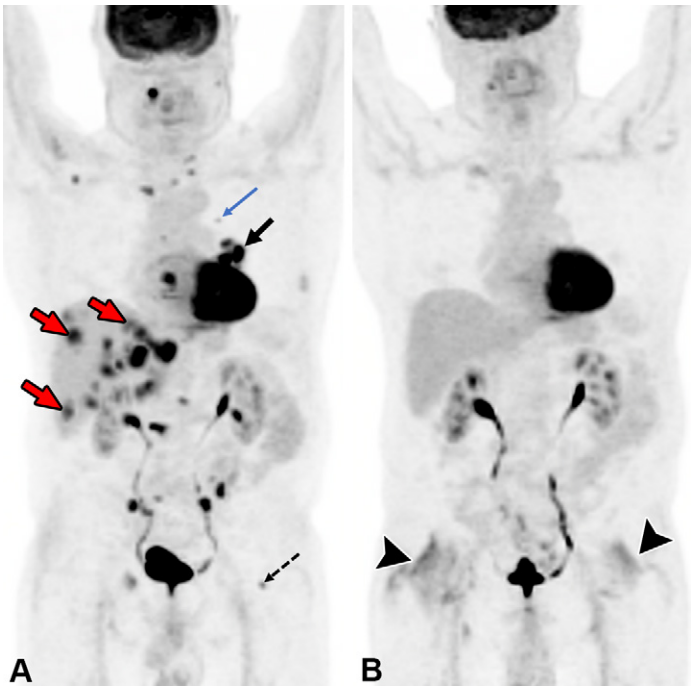


Figure 12. Poorly differentiated carcinoma of the left lung in a 77-year-old man. **(A)** MIP FDG PET image for staging shows increased FDG uptake in the left lung mass (solid black arrow), multiple liver lesions (red arrows), and extensive osseous (dashed arrow), pulmonary (blue arrow), and cerebral metastases. The patient was started on pemetrexed and pembrolizumab and underwent whole-brain irradiation for the cerebral metastases. **(B)** MIP FDG PET image 1 year after the baseline study shows complete metabolic resolution of the previously seen lesions. The moderately increased FDG uptake in the periarticular region of both hips (arrowheads) likely represents immune-related arthritis.

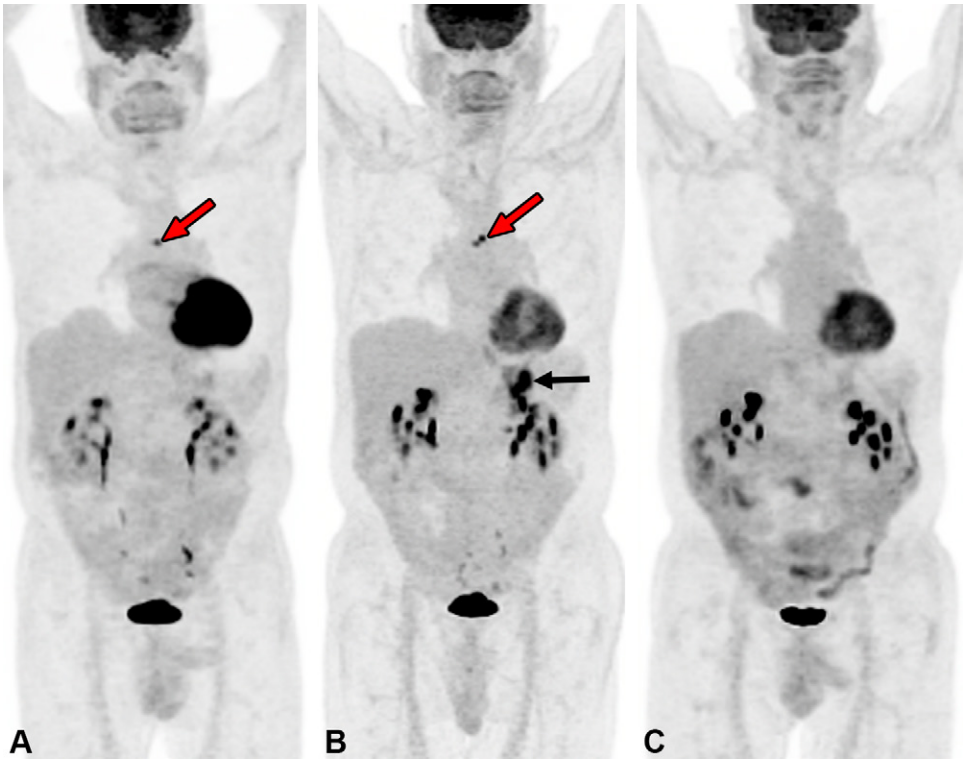


Figure 13. Diffuse large B-cell lymphoma with prior treatment failure in a 52-year-old man who underwent chimeric antigen receptor T-cell therapy. **(A)** MIP FDG PET image obtained during the course of treatment for response evaluation shows complete metabolic resolution of the abdominal and retroperitoneal lesions, with only the lower paratracheal lymph node (arrow) showing hypermetabolism. This was consistent with PMR (Deauville score, 4). **(B)** MIP FDG PET image 3 months later for end-of-treatment response assessment shows an interval appearance of FDG avidity in the abdominal and retroperitoneal lesions (black arrow), with an increase in size and avidity of the lower paratracheal lymph node (red arrow). **(C)** MIP FDG PET image 7 weeks later to differentiate pseudoprogression versus true progression shows metabolic resolution of the abdominal and retroperitoneal lesions and the lower paratracheal lymphadenopathy; these findings are consistent with the pseudoprogression seen on the interim study.

(51). The pathophysiologic basis of hyperprogression is not entirely clear, although the interaction of anti–PD-1 with tumor-associated macrophages, promoting an immunosuppressive microenvironment, has been proposed (52).

Dissociated Response

A dissociated or mixed response is seen when some lesions respond to therapy while others do not (Fig 15). A dissociated response is also seen with conventional cytotoxic therapy; this results from inherent interlesion heterogeneity, the existence of synchronous malignancies, or the treatment-induced emergence of resistant tumor clones (3,53,54). This response pattern with immune checkpoint inhibitor therapy likely reflects the interlesional heterogeneity whereby select tumors acquire resistance to specific immune-targeting pathways by way of additional genetic mutations (55). FDG PET/CT can be helpful in identifying dissociated response by demonstrating persistent metabolic activity in residual masses that are resistant to treatment or the development of new lesions that are consistent with the primary disease. Additional local

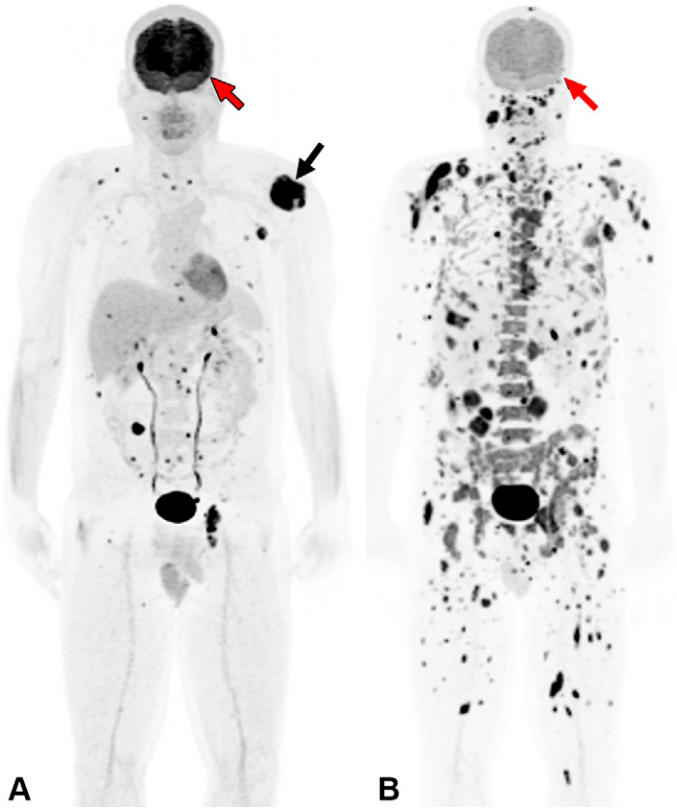


Figure 14. Melanoma of the left posterior shoulder and a biopsy-proven metastatic left axillary lymph node in a 44-year-old man. **(A)** MIP FDG PET image for initial staging shows the primary tumor (black arrow) and multiple nodal, soft-tissue, pulmonary, and osseous metastases. Partial resection of the left trapezius muscle with skin grafting was performed, and the patient was started on combination therapy with nivolumab and ipilimumab. **(B)** MIP FDG PET image for response assessment after four cycles of therapy, obtained 3 months after the baseline study, shows interval development of multiple FDG-avid lesions throughout the body, suggesting hyperprogression. Note that there appears to be a tumor-sink effect at follow-up imaging, as evidenced by reduced FDG uptake in the brain (red arrow) by about 25% and at other physiologic sites.

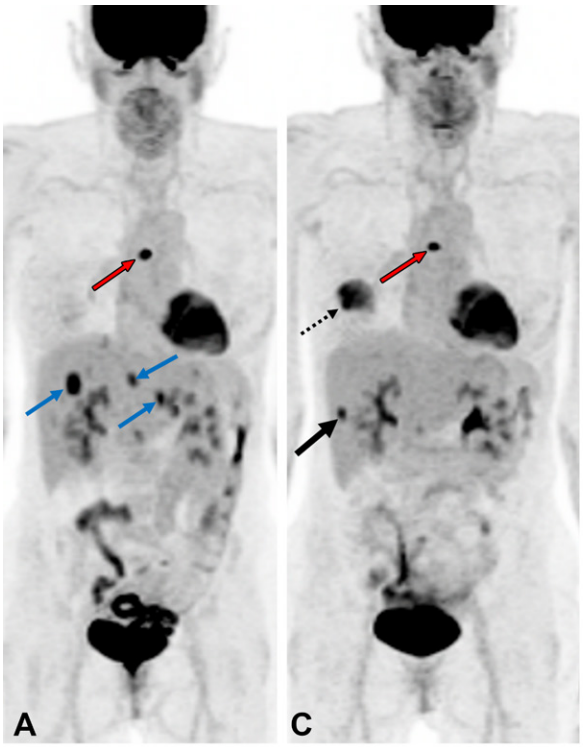
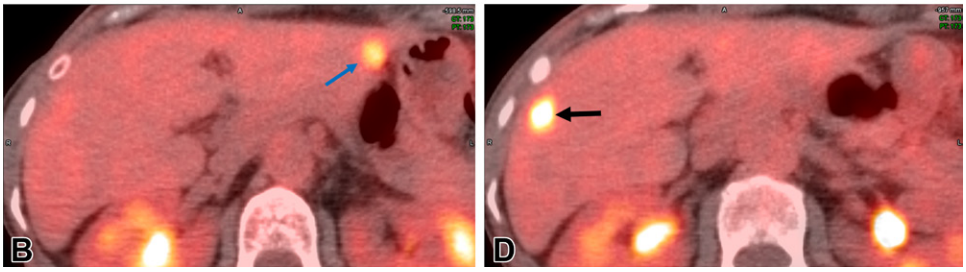


Figure 15. Pulmonary metastases seen after resection of urothelial melanoma in a 64-year-old woman, who was started on pembrolizumab. **(A, B)** MIP FDG PET **(A)** and fused FDG PET/CT **(B)** images for response evaluation during treatment show multiple hypermetabolic liver lesions (blue arrows) and a subcarinal lymph node (red arrow in **A**). **(C, D)** MIP FDG PET **(C)** and transaxial fused FDG PET/CT **(D)** images 3 months later for response evaluation at the end of treatment show metabolic resolution of all previously seen hepatic lesions and a mild reduction in FDG avidity of the subcarinal lymph node (red arrow in **C**), with the SUV_{max} reduced to 10.4 (from 15.5 previously). However, there is interval development of a hypermetabolic lesion (solid black arrow in **C**, arrow in **D**), which was not seen previously, in liver segment V, representative of a dissociated or mixed response. Note the development of a focal right lung consolidation secondary to postobstructive pneumonia (dashed arrow in **C**).



therapy may be instituted accordingly for these lesions, when appropriate.

Response Assessment in Clinical Practice

Response assessment criteria are useful in the research setting, but their principles can be applied to routine clinical practice as well. For example, interim FDG PET/CT is used in patients with HL and several NHLs for early monitoring of treatment response and to decide the further treatment course. The interpretation of both interim and end-of-treatment PET findings is based on the Lugano criteria with use of Deauville scores. While this assessment is mainly visual, at times it might be difficult to interpret certain response categories, such as those defined by a Deauville score of 3, for which the interpretation depends on the clinical context.

In scenarios in which treatment de-escalation is being contemplated, interpreting a Deauville score of 3 as non-CR might be beneficial to avoid potential undertreatment. Conversely, in scenarios in which treatment escalation is planned, interpreting a Deauville score of 3 as CR might help avoid potential overtreatment. Thus, there lies some subjectivity in the interpretation of these cases, and a patient-specific approach (partly based on the therapeutic goals and risks) might work better. It is important to communicate the scan results in an individualized manner to the treating physician instead of using a "one-size-fits-all" approach.

For solid malignancies, the treatment response is frequently assessed by using the anatomic changes in the lesions and the changes in SUV_{max} from the baseline. The principles of PERCIST help us appreciate the non–treatment-related variabilities in SUVs. Thus, it is typically not prudent to attribute small changes in SUV_{max} (in the absence of any significant changes in lesion size) to treatment response. Conversely, in the setting of immunotherapy, one should be mindful of pseudoprogression and recommend reassessment to confirm the findings. An attempt should be made to adhere to consistent study techniques and patient preparations (Table 3) to improve the accuracy of response assessments. It is also important to recognize that FDG PET/CT, like any other diagnostic modality, has a lower limit of detectability. Thus, lesions that are negative at PET might harbor residual tumor that has insufficient volume or metabolic activity to be detected. Finally, it must be recognized that response assessment is a continuum, and while the conventional response categories are used for simplicity and ease of communication, other aspects, especially the timing of response, also should be taken into account to get a more complete picture.

Conclusion

FDG PET/CT captures the early changes in glucose metabolism that accompany response to treatment. These metabolic alterations often precede anatomic changes and can be used for early response assessment in lymphoid and solid malignancies. Response assessment criteria help define optimal thresholds for response categories, with the goal of accurately predicting long-term survival outcomes. Thus, objective response assessment represents a vital component of therapeutic trials, and efforts to improve the predictive capabilities of response assessment criteria are ongoing.

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