^{18}F-Fludeoxyglucose PET/Computed Tomography for Assessing Tumor Response to Immunotherapy and Detecting Immune-Related Side Effects

A Checklist for the PET Reader

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KEYWORDS

• FDG • PET • Immunotherapy • Immune-related side effects • Pseudoprogression • Hyperprogression • Therapy monitoring

KEY POINTS

- ^{18}F-Fludeoxyglucose PET is the only imaging modality capable of visualizing treatment response to immunotherapy, signs of immune activation (spleen uptake and so forth), and immune-related side effects.
- Because it is known that patients experiencing immune-relate side effects are more likely to respond to treatment, discriminating between pseudoprogression and real progression and identification of hyperprogression is key for patient care.
- Conventional PET criteria (European Organization for Research and Treatment of Cancer and PET Evaluation Response Criteria In Solid Tumours) can overlook pseudoprogression, leading to the use of immune-modified PET criteria.

BACKGROUND

Immune Checkpoint Inhibitors

Immunotherapy, which radically differs from other strategies in relying on the reactivation of the immune system to recognize and kill cancer cells, has recently emerged as an important advance in cancer treatment.[1] The use of immunomodulatory monoclonal antibodies that directly enhance the function of components of the antitumor immune response, such as T cells, or block immunologic checkpoints that would otherwise restrain effective anti-tumor immunity, has recently been actively investigated in oncology.

To date, the main immunotherapeutic approach that has been translated into survival benefit and is currently used in practice is the blockade of immune checkpoints. Broadly, the 2 most effective classes of agent are directed, alone or in combination, toward cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or the programmed cell death protein 1 (PD1) or the PD1/programmed cell death protein ligand 1 (PD1/PD-L1) axis, which are negative regulators of T-cell immune function.[2]

The CTLA-4 inhibitor, ipilimumab, has been shown to improve survival rates in melanoma patients. PD1/PD-L1 inhibitors (of which the first

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validated agents were pembrolizumab and nivolumab) have been shown to improve survival rates among patients with various tumor types, including melanoma, lung, head and neck, and bladder cancers. Typically, these drugs are given intravenously every 2 to 3 weeks, and a durable complete response has been observed in a variable but small proportion of patients. Patients whose tumors or immune cells express PD-L1 have a higher likelihood of benefiting from treatment with PD1/PD-L1 inhibitors, although PD-L1-negative patients have also been shown to respond.

Because not all patients respond to single-agent immunotherapy, hundreds of combination trials are ongoing. At the time of the writing of this article, more than 2916 trials using immunotherapy are listing on clinicaltrial.gov. Among these trials, 23 use ^{18}F-Fludeoxyglucose (FDG) PET as a tool for therapy monitoring. Different combination strategies are under investigation, including with standard chemotherapy, targeted agents, and antiangiogenic agents. Because radiation induces the release of tumor antigens, also known as neoantigens, there is strong rationale supporting the use of combinations of external and immune checkpoint inhibitors, with patients benefiting from the so-called abscopal effect.[3]

Immune-Related Side Effects

By reactivating the immune system, these immunotherapies have led to the development of new toxicity profiles, also called immune-related adverse events (irAE). IrAEs can involve many organ systems, and their management is radically different from that of adverse events from cytotoxic drugs.[4] There is a wide variety of irAEs, with the endocrine, lung, cutaneous, and gastrointestinal systems being the most commonly affected. The irAE pattern is different across immune checkpoint inhibitor classes and could be driven by the different patterns of immune cell activation that can occur with different classes of immune therapy.[5] The rapid identification of these irAEs and treatment with corticoids[6,7] can improve patient outcomes, without reduction in treatment efficacy.[8,9]

Other details on available inhibitors, their biologic rationale, and irAE can be found elsewhere.[10–16]

Pseudoprogression and Hyperprogression

Different patterns of response to immunotherapeutic agents were also observed from those to chemotherapeutic and molecularly targeted agents. First, responses usually occur early, but can also be delayed. Second, responses may be preceded by apparent disease progression, defined as pseudoprogression. These patterns of response were mainly initially reported in patients with melanoma receiving anti-CLTA4 agents, with approximately 15% of patients experiencing pseudoprogression,[17] and led to adapted morphologic criteria on computed tomography (CT), namely the irRECIST criteria.[17–19] Tumors other than melanoma show lower cases of pseudoprogression (<3%), especially with the use of anti-PD1/PD-L1 agents.

More recently, hyperprogression was described as an acceleration of tumor growth kinetics.[20,21] Indeed, some phase 3 trials have illustrated worse overall survival rates in patients receiving immune checkpoint inhibitors than in control patients during the first few months, supporting the concept of hyperprogression.[19,22] Although these studies had no control arm, they suggested that immunotherapy might be detrimental in some patients with cancer.[20,21,23]

^{18}F-Fludeoxyglucose PET for Immunotherapy Response Assessment: Evolution of Metabolic Response Criteria

The first PET-based response criteria were proposed by the European Organization for Research and Treatment of Cancer (EORTC) in 1999,[24] and The PET Evaluation Response Criteria In Solid Tumours (PERCIST) were later published in 2009.[25,26] PERCIST are rather similar to the EORTC criteria, and these criteria often produce very similar results, with agreement reported to range between 0.76 and 1.[27] Whereas EORTC is based on the use of maximum standardized uptake value (SUV_{max}), PERCIST recommend SUV lean (SUV normalized by lean body mass, or SUL) for the assessment of tumor response and the identification of a minimum tumor SUL equivalent to 1.5 times the mean SUL of the liver for a lesion to be selected as target lesion. PERCIST also recommend the measurement of SUL in up to 5 tumors (up to 2 per organ). The latter were also the first criteria using SUL_{peak}, which can be measured within a 1-cm^3 spherical volume of interest (VOI).

The EORTC criteria do not specify the number of lesions to be measured or the minimum measurable lesion uptake, whereas PERCIST have requirements regarding target selection (typically the hottest lesions, from 1 to 5 and no more than 2 per organ). For PERCIST criteria, the measurable target lesion is the single most intense tumor site on pretreatment and posttreatment scans, which means that the target lesion may receive different pretreatment and posttreatment.

Based on the SUL_{peak} and SUV_{max} variation between the pretreatment and posttreatment scans, patients were classified according to PERCIST and EORTC as follows:

- *Complete metabolic response*: complete resolution of ^{18}F-FDG uptake in the tumor volume, with tumor SUL lower than liver SUL and background blood pool, and disappearance of all lesions if multiple.
- *Partial metabolic response*: at least 30% (PERCIST) or 25% (EORTC) reduction in tumor uptake.
- *Stable metabolic disease*: less than 30% (PERCIST) or 25% (EORTC) increase, or less than 30% or 25% (EORTC) decrease in tumor ^{18}F-FDG SUL_{peak} and no new lesions.
- *Progressive metabolic disease* (PMD): greater than 30% (PERCIST) or 25% (EORTC) increase in ^{18}F-FDG tumor SUL_{peak} within the tumor or appearance of new lesions.

Because of the change of patient classification after the appearance of a new lesion as PMD for both EORTC and PERCIST, these criteria would be misled in the case of pseudoprogression. Indeed, the EORTC criteria were the first to be applied for the assessment of response of solid tumors to immunotherapy. In that first report, the investigators recognized the appearance of new lesions, conventionally defining disease progression as being a potential cause of response misclassification that occurred in 4 out of 22 melanoma patients scanned after 2 cycles of Ipilimumab.[28]

Within the last few years, several modified PET evaluation criteria have been proposed, mainly in series of melanoma patients receiving Ipilimumab.[28–32] This article does not aim to describe these studies in detail; they can be found in the recent report of the European Association of Nuclear Medicine on immunotherapy assessment.

To briefly summarize, efforts tended to better evaluate the whole tumor burden and not be misled by the appearance of new lesions wrongly classifying patients experiencing pseudoprogression as PMD. Most of the published series included a limited number of patients and focused on melanoma patients receiving ipililumab.

PERCIST were the most heavily studied criteria, because they recommend to select up to 5 (hottest) lesions, which can be adapted to search for new lesions deemed to be pseudoprogressive. Several investigators also advised an early follow-up study to confirm or exclude pseudoprogression.

RECOMMENDATION ON PET SCANNING AND REPORTING

PET Protocol

First, it is important to remember patients should be scanned on the same PET system for baseline and posttreatment scans, because it is known that reconstruction inconsistencies may strongly alter EORTC and PERCIST classification. This issue would obviously also apply to modified PERCIST criteria.

Apart from the usual compliance to PET tumor imaging guidelines and harmonizing standards, several points regarding the PET acquisition protocol need to be raised.[33–35] First, although including the brain in the field of view is not systematic for most of the PET centers, the skull base should be included, so that immune-related side effects involving the pituitary gland are observed (**Fig. 1**A, B). Second, in patients with melanoma with a primary location in the lower limbs, a whole-body acquisition is recommended (**Fig. 1**C, D).

The number of cycles of immunotherapy since the baseline PET scan and the date of the last infusion are also given. Patients may have received several lines of immunotherapy, for example, because they experienced a toxicity requiring a first line to be withdrawn, and are rechallenged with another drug after recovery of irAEs.

When to Perform ^{18}F-Fludeoxyglucose PET?

FDG PET imaging should be performed before the start of immunotherapy. The metabolic information obtained at this time allows adequate restaging and proper evaluation of disease extent at baseline. Based on a given tumor board, the scan can be repeated at the first treatment response evaluation, which in most cancer types is 8 or 9 weeks after the start of immunotherapy (generally after 2 or 3 cycles of treatment), depending on the regimen used. It is noteworthy that some patients receiving nivolumab may receive a flat dose by injection every 4 weeks. In that case, patients receive the same total dose as for the 2-week injection period, and it can be recommended to scan them after a single injection if early therapy assessment is required. Subsequent imaging with FDG-PET is recommended regularly during treatment and at the end of immunotherapy, before treatment stops.

In the case of irAEs, which are very likely to be visualized on PET imaging, FDG PET can be used after treatment withdrawal and/or corticosteroids treatment, to check whether the side effects have been resolved and to be used as a new baseline scan before rechallenging with

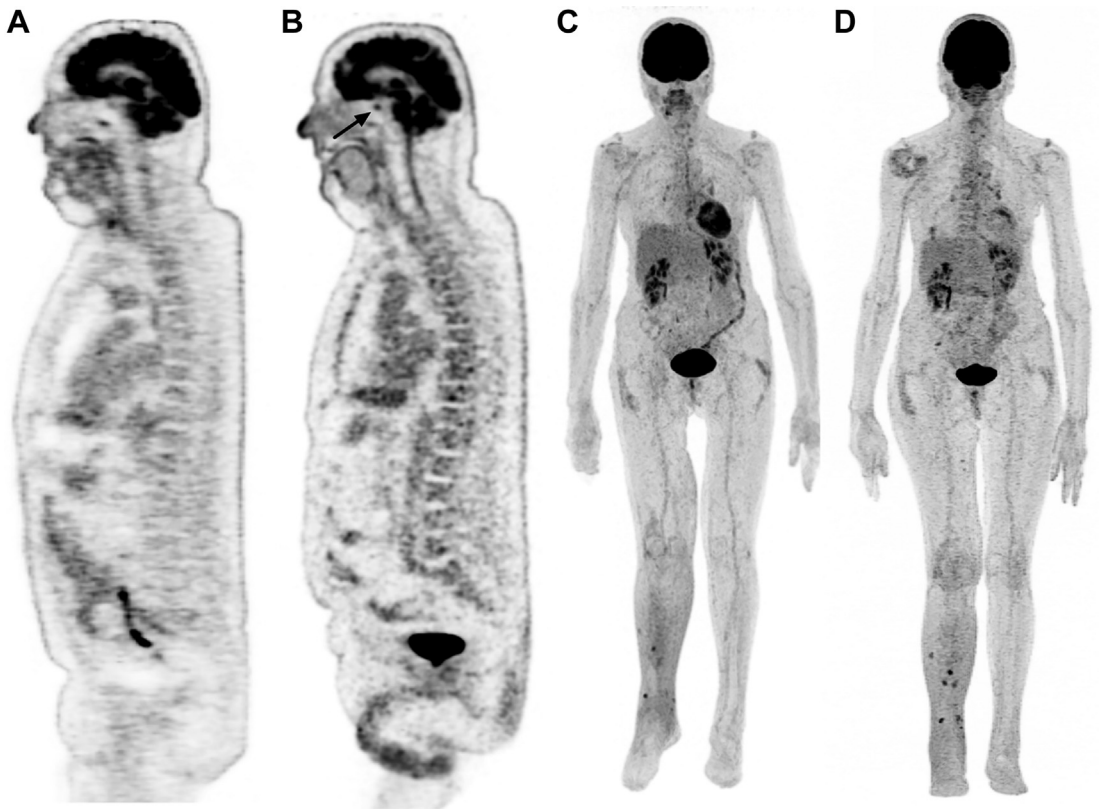


Fig. 1. PET protocol. Serial sagittal ^{18}F FDG PET and PET-CT, including the skull in different phases of the disease in a 74-year-old man affected by a metastatic melanoma of the right thigh. (*A*) Baseline before introduction of immunotherapy and (*B*) after 6 courses of nivolumab, showing a related hypermetabolism in the pituitary gland (*arrow*) owing to nivolumab toxicity in an asymptomatic patient. Serial ^{18}F FDG maximum intensity projection (MIP), including the skull and lower limbs in different phases of the disease in an 82-year-old woman affected by a melanoma of the right ankle with in transit metastases of the right lower limb and the lung. (*C*) Baseline before introduction of immunotherapy and (*D*) after 2 courses of nivolumab, showing a metabolic progression in the right lower limb and lung.

immunotherapy or the start of another line of treatment, whether it is chemotherapy or tyrosine kinase inhibitors.

How to Assess and Report Immune-Related Signs

Inflammatory reactions can occur during the treatment and are associated with high glucose consumption, which may be associated with pseudoprogression and irAEs and can lead to misinterpretation of FDG PET images. Response assessment during immunotherapy can therefore be rather challenging. However, FDG PET can show dynamic adaptation of the immune response to checkpoint inhibitors.[36,37] Moreover, being a whole-body modality, it also allows precise localization of irAEs, which can occasionally become life-threatening; for example, colitis, pneumonitis, and pancreatitis. Furthermore, the occurrence of irAEs and the possibility of detecting them on PET may be an additional factor predicting response to immunotherapy, given the evidence that appearance of irAEs is associated with a better response to PD1 inhibitors in patients with melanoma or NSCLC.[14,38]

Although potentially immune-related inflammatory findings on FDG PET should be reported, these will not necessarily be associated with clinical symptoms (ie, irAEs). However, clinicians should be made aware of their presence so that complementary tests and clinical monitoring can be performed, because medical intervention may be necessary in selected cases. **Fig. 2**A–C displays colitis, whereas **Fig. 2**D–F illustrates a metformin-induced pseudocolitis pattern.

The first sign of immune activity to be checked is spleen enlargement and/or increased uptake leading to an inversion of the liver-to-spleen uptake ratio (**Fig. 3**). Reactive nodes in the drainage basin of

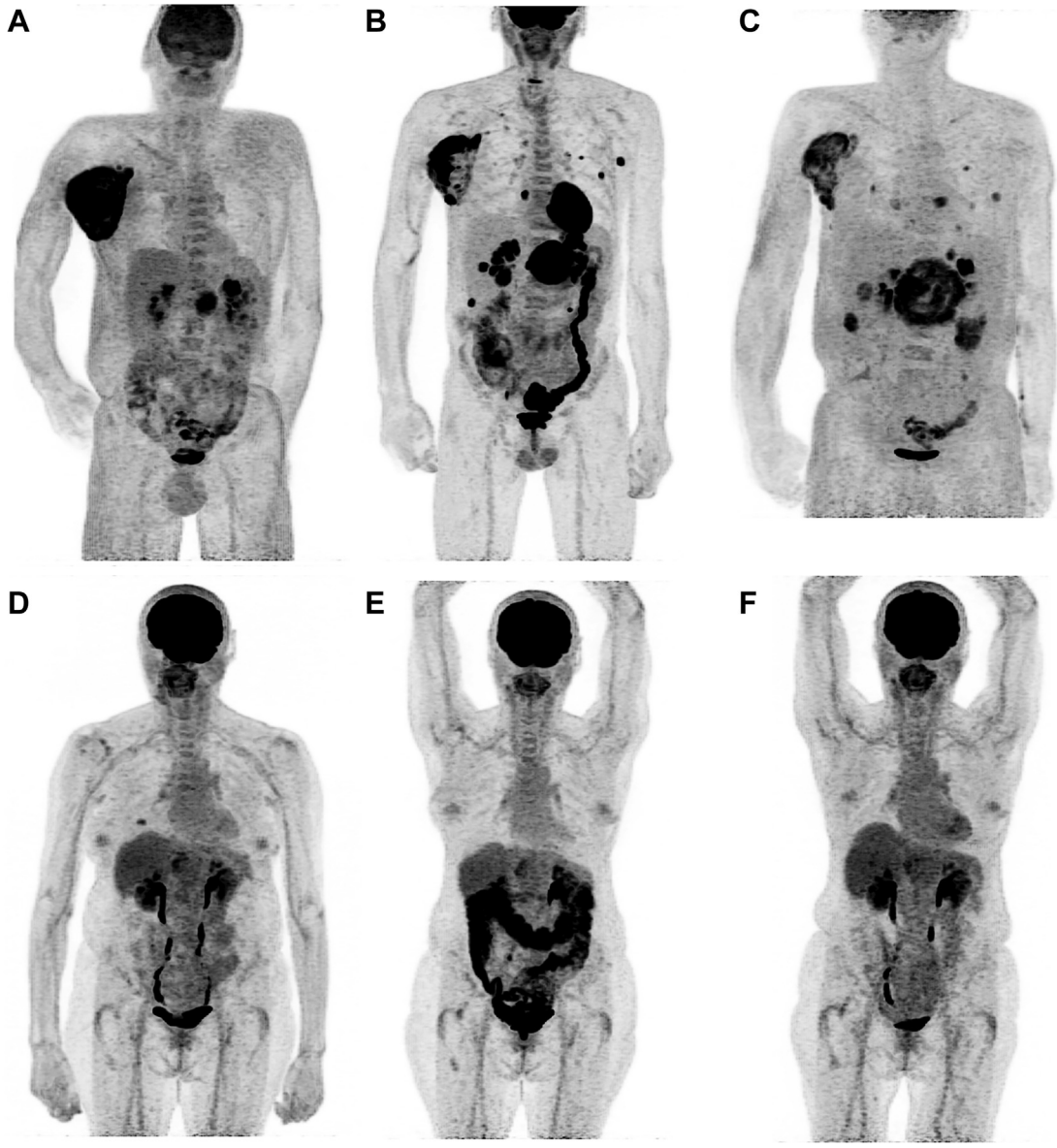


Fig. 2. Seeking immune-related side effect on FDG PET: beware of the outlier! Serial ^{18}F FDG MIP in different phases of the disease in a 65-year-old woman affected by a choroid melanoma with hepatic lymph node involvement. (*A*) PET after 6 courses of pembrolizumab, (*B*) PET after 8 courses of pembrolizumab, showing a diffuse colic hypermetabolism with diarrhea related to immunotherapy toxicity, confirmed by endoscopy-guided biopsies, leading to the withdrawal of pembrolizumab and the use of corticosteroids. (*C*) Patient was switched to nivolumab and FDG PET after 1 course of nivolumab allowed checking for the absence of any recurrence of the colitis. Serial ^{18}F FDG PET in different phases of the disease in a diabetic 59-year-old man affected by a metastatic melanoma under metformin. In most of the PET centers, withdrawal of metformin is planned to avoid intense uptake in the colon and small bowel. (*D*) PET baseline before introduction of immunotherapy with 1.34 g/L of glycemia. (*E*) PET after 2 courses of pembrolizumab, showing a diffuse colic hypermetabolism thought to be irAE colitis. However, the endoscopy was normal, and normal glycemia (0.65 g/L) at the time of the interim PET was likely due to a lack of observance of the recommended discontinuation of metformin 2 days before the FDG PET/CT. (*F*) PET after 5 courses of pembrolizumab showing the absence of colic hypermetabolism with 1.92 g/L of glycemia.

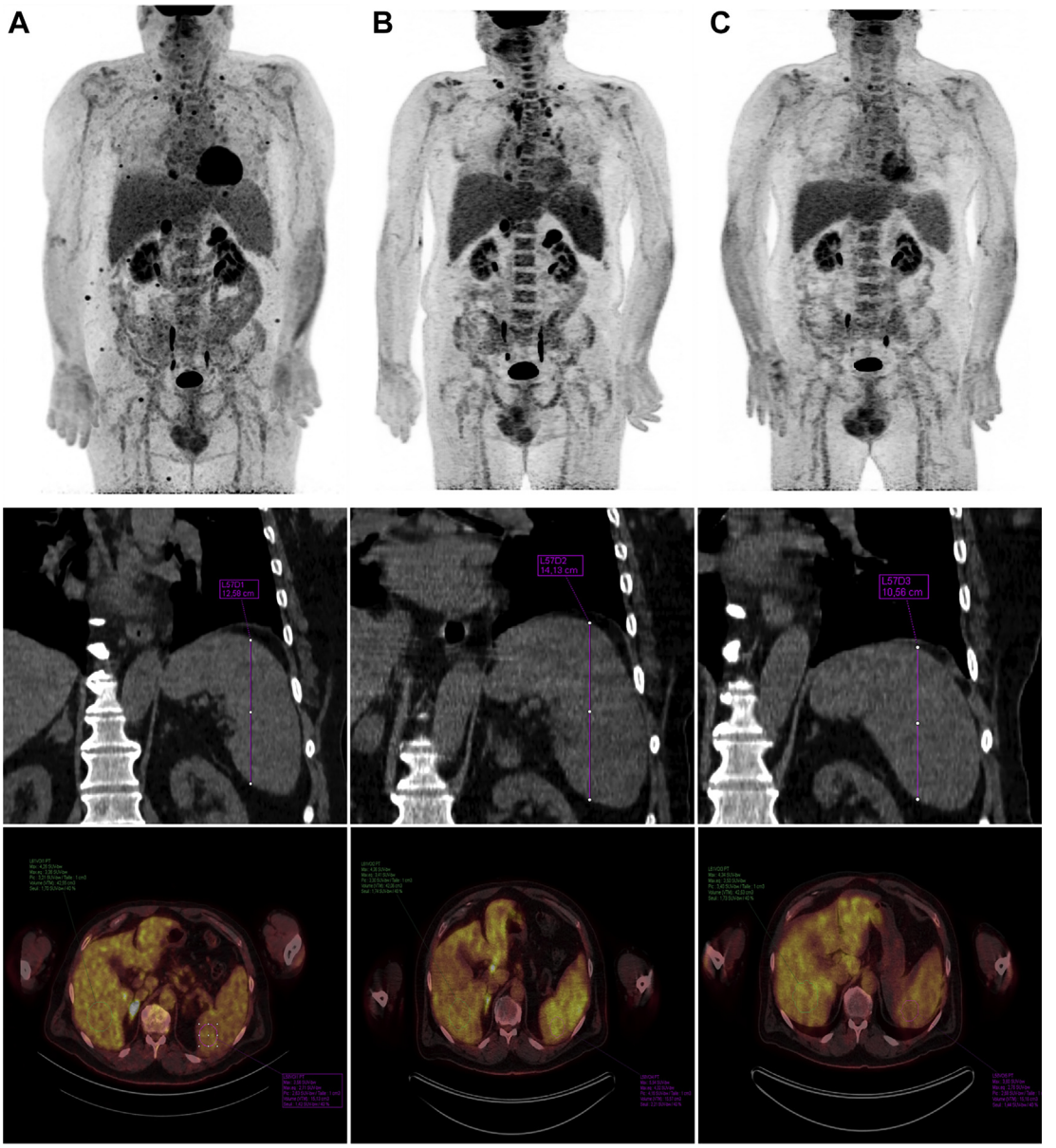
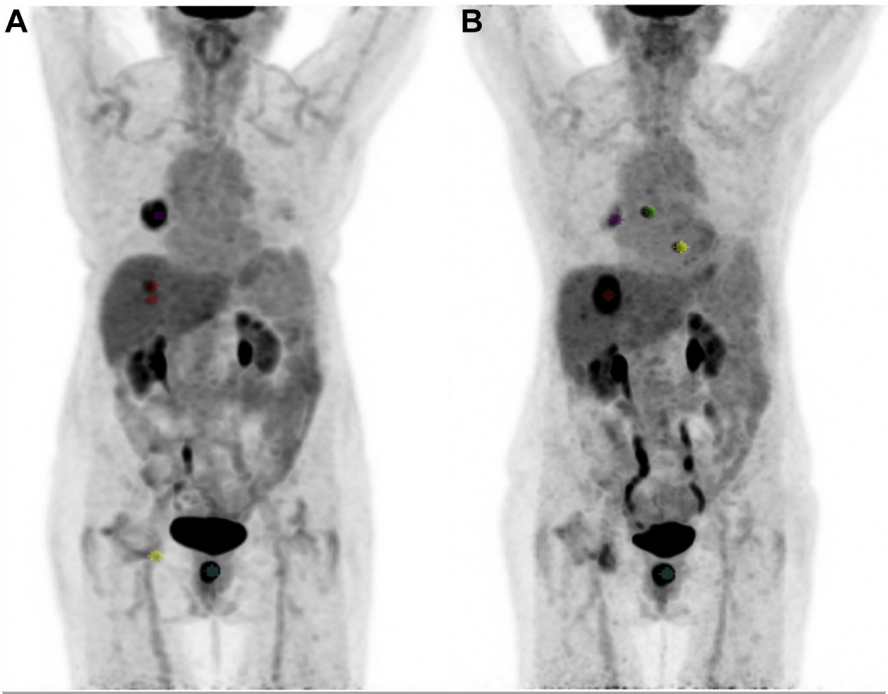


Fig. 3. How to seek immune activation on FDG PET. Serial ^{18}F FDG PET/CT in different phases of the disease in a 61-year-old man affected by a melanoma of the left forearm with subcutaneous lymph nodes and bilateral adrenal glands involvement. (*A*) Baseline PET before introduction of immunotherapy and (*B*) after 2 courses of nivolumab, showing diffuse osteomedullary hypermetabolism, an inversion of the spleen-to-liver ratio associated with an increase in the spleen dimensions in line with a lymphocyte activation. This pattern precedes (*C*), an excellent partial metabolic response that is observed after 5 courses of nivolumab in all lesions.

the primary tumor may also be seen. To date, there are no consensus guidelines on how to report spleen uptake. Also, uptake in other lymphoid organs has been reported, namely, thymus, ileocecal valve, and healthy bone marrow.[36] In their study, Seban and colleagues[39] reported the use of SUV_{max} obtained with a 2-cm VOI for the spleen and a 15-mm VOI placed at the center of the first lumbar vertebrae for bone marrow. The investigators also used a 3-cm VOI in the liver to compute spleen-to-liver ratio and bone marrow-to-liver ratio. In this way, the liver VOI may also be used for PERCIST or immune-modified PERCIST. Therefore, although reporting multiple target of immune activation is likely to be time consuming in routine practice, the authors suggest that the



Target	Baseline EARL SUL peak		Interim EARL SUL peak	
1	15.32	Anal	17.41	Anal
2	5.59	Lung	7.77	Hepatic
3	2.85	Hepatic	2.55	Lymph Node
4	2.35	Hepatic	2.3	Lung
5	1.12	Bone	2.3	Bone
	27.23		**32.33 : △ -18.72%**	
PERCIST5			**PMD**	
imPERCIST5			**SMD**	

Fig. 4. Evaluating tumor response: PERCIST versus immune-adapted PERCIST. Serial ^{18}F FDG MIP in different phases of the disease in a 73-year-old woman affected by a melanoma of the anal canal with lung and lymph node hepatic metastasis. (*A*) PET baseline before introduction of immunotherapy and (*B*) after 6 courses of nivolumab, showing the appearance of new lesions. This pattern classifies the patient with PMD according to the PERCIST5 criteria, but stable metabolic disease is found when using imPERCIST5. EARL, EANM Research Ltd; SMD, stable metabolic disease.

PET reader could report SUV metrics in 2 VOIs in the liver and in the spleen at the same level and compute the liver-to-spleen ratio (see **Fig. 3**).

Because every organ can be involved by the immune infiltrate, it is important to use the baseline scan data not only to compare changes in uptake in the target lesions but also to check that intense uptake deemed to be an immune-related sign was not present on the baseline scan. On the contrary, diffuse and intense uptake in these organs is likely to be an immune-related sign.

One should also consider whether the pattern of new nodal uptake suggests sarcoidosis, especially bilateral hilar and mediastinal uptake associated with portocaval nodal uptake.

Therapy Assessment

Depending on the availability of the SUV_{peak} metric on the workstation used, either the EORTC PET response criteria or PERCIST can be used to report FDG uptake changes in target lesions. However, care should be taken when reporting PET results in patients in whom disease progression is suspected, because of the difference in patterns of response to immunotherapy from

those to conventional chemotherapy and other molecularly targeted therapies, especially during the first few cycles of treatment. One should be aware of the possibility of pseudoprogression, having in mind that this should only be considered when the clinical condition of the patient is concomitantly improving. In patients whose clinical condition is not improving and who have disease progression on imaging, one should discontinue immunotherapy. The risk of continuing treatment beyond progression is that it may prevent commencement of a new line of treatment once the progression is confirmed because of clinical deterioration.

In patients with apparent disease progression, the number and location of new lesions should be reported, excluding pathologic foci in organs deemed to be due to the immune infiltrate. Indeed, a recent study suggested that the appearance of 4 or more new lesions of less than 1 cm in functional diameter or 3 or more new lesions of more than 1 cm in functional diameter is likely to be due to a real progression rather than pseudoprogression.[31]

The PET reader should be aware of the importance of interrupting treatment early if hyperprogression is suspected, because this pattern is more frequent in elderly patients.

As far as selecting which criteria should be used, several series have reported various modifications of PERCIST. However, none of them have proposed a recommended use for daily practice. However, as PERCIST have become used more and more often for the evaluation of chemotherapy and molecularly targeted therapy, the authors think that it is appropriate for the PET community to use these modified criteria, especially in the case where patients' progression is suspected based on the appearance of new suspicious lesions. In this case, it can be recommended to use imPERCIST,[40] where the 5 hottest lesions are selected and a new hot lesion would not classify the patient as PMD, unless the variation in the sum of the 5 hottest lesions between baseline and interim PET is greater than 30% (**Fig. 4**). Gathering, pooling, and analyzing that kind of data within national or international observational studies, in addition to the metrics mentioned in later discussion, would be a useful way of improving the use and the visibility of FDG PET for therapy assessment in patients receiving immunotherapy.

Perspectives

In addition to conventional SUV metrics, one could consider recording metabolic active tumor volume (MATV) and Total Lesion Glycolycis (TLG) before and after treatment,[41,42] again excluding uptake in organs deemed to be due to the immune infiltrate. Indeed, MATV could be seen as the PET counterpart of iRECIST, where the sum of all lesions is used. More recently, PET texture analysis (TF)[43,44] has emerged in the field of cancerology and has shown promising results in predicting response to treatment and as a risk stratification tool. In addition to their potential role as prognosticators, FDG PET heterogeneity parameters in differentiating between pseudoprogression and real progression could be evaluated, on the basis that pseudoprogressing lesions, because of the immune infiltrate, may harbor different TF patterns.

The recent evolution in PET images analysis based on machine learning and central neutral network could make computation of MATV and TLG easier. In particular, automatic or semiautomatic computation of tumor MATV/TLG and splenic MATV/TLG would be useful to the PET reader to assess the whole tumor burden together with signs of immune activation, while maintaining the throughput of a busy PET center.

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