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EDITORIAL

Immunotherapy and ^{18}F-FDG PET/CT: standardised procedures are needed

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Immune checkpoint inhibitors are a revolutionary cancer treatment, demonstrating remarkable efficacy and manageable toxicity with dramatic clinical results, particularly in patients with melanoma and lung cancer [1, 2]. Several case studies involving patients affected by cutaneous melanoma, lung cancer, lymphoma and other solid tumours undergoing or candidates for immunotherapy and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) have been published [3–12]; however, many inconsistencies in the treatment response assessment by PET/CT in patients undergoing immunotherapy can be found in the literature and in clinical practice. The main question is "when and how should ^{18}F-FDG PET/CT be performed during immunotherapy?"

First, some papers have discussed the usefulness of ^{18}F-FDG PET/CT in predicting the response to immunotherapy. In the study by Grizzi et al. [8], in patients affected by lung cancer, a low maximum standardised uptake value (SUVmax) in the primary tumour was associated with a fast disease progression during immunotherapy. Moreover, Evangelista et al. [13] found that a widespread lung disease with a high tumoural burden (evaluating by whole-body SUVmax or whole-body SUVmean) was correlated with the failure of immunotherapy, especially in female patients. No data about the prediction of response to immunotherapy and ^{18}F-FDG PET/CT are available in other solid tumours (i.e. breast cancer, mesothelioma, or others), representing an important point of view.

Second, the timing between immunotherapy administration and ^{18}F-FDG PET/CT scanning is variable (at least 10 days or 15 days or 21 days) since no recommendation is given in the published reports. Moreover, the ideal timing between ^{18}F-FDG PET/CT scanning and immunotherapy cycles, both interim and the end, is unclear. By analysing the published literature, heterogeneous conclusions can been drawn about the interval period between immunotherapy administration and the evaluation of response to therapy by ^{18}F-FDG PET/CT. Cho et al. [3] prospectively enrolled 20 patients with cutaneous melanoma who underwent ^{18}F-FDG PET/CT at baseline, after 21 days and after 4 weeks from the administration of immunotherapy, showing the potential of ^{18}F-FDG PET/CT combined with anatomical data to predict early the response to therapy. In the FIR trial, ^{18}F-FDG PET/CT was performed prior to treatment and 6 weeks after immunotherapy [12], reporting a higher objective response rate in patients with metabolic response by European Organisation for Research and Treatment of Cancer (EORTC) criteria than in metabolic non-responders. Probably, the three scan time-points are necessary to evaluate the effective response to immunotherapy, at baseline, after 2 weeks and 6 weeks to minimise false-positive findings in case of pseudo-progression.

Third, different criteria have now been tested for the evaluation of response to immunotherapy by ^{18}F-FDG PET/CT, although none has been validated and identified as a standard. Table 1 reports the main proposed criteria and their characteristics [3, 4, 11, 14].

Fourth, clinical assessment and radiological images are now considered the standard for the evaluation of response to immunotherapy. However, some limitations are associated with both, particularly in patients with no response to immunotherapy. Neither clinical nor radiological assessment can distinguish a real progression from pseudo-progression, especially in case of the appearance of immune-related side

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Table 1 Summary of available criteria for the evaluation of response to immunotherapy

Criteria, ref	Neoplasia	N pts	Explanation
PECRIT [3]	Melanoma	20	Combined RECIST 1.1 and PERCIST
PERCIMT [4]	Melanoma	41	Two categories: (1) clinical benefit, comprised SD, PR or CR, and (2) no clinical benefit, considered PD (i.e., new lesions with a functional diameter > 1 or 1.5 cm)
iPERCIST [11]	Lung cancer	28	Two new categories replacing the PMD category: unconfirmed progressive metabolic disease (UPMD) and confirmed progressive metabolic disease (CPMD). UPMD was a PMD at SCAN-2, and CPMD was an UPMD confirmed 4 weeks later at SCAN-3. In iPERCIST, SCAN-3 is compared to SCAN-2, and patients were classified as CMR, PMR, SMD, or CPMD, according to PERCIST recommendations
Modified Lugano criteria [14]	Lymphoma	NA	The term "indeterminate response" was introduced to identify unclear lesions until confirmed as flare/pseudo-progression or true PD by either biopsy or subsequent imaging

PECRIT PET/CT criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy, *PERCMIT* The *PET* Response Evaluation Criteria for Immunotherapy, *iPERCIST* immune-PET response criteria in solid tumours, *SD* stable disease, *PR* partial response; *CR* complete response, *PD* progressive disease, *PMD* progressive metabolic disease, *NA* not available

effects. Two papers have recently been published on the utility of ^{18}F-FDG PET/CT for the evaluation of response to immunotherapy in patients with a suspected progressive disease in clinical evaluation or radiological imaging [5, 10]. In both cases, ^{18}F-FDG PET/CT seems able to predict the response to immunotherapy, with a clear effect on prognosis.

In our opinion, an effort should be made to define the role of ^{18}F-FDG PET/CT in the evaluation of response to immunotherapy. Metabolic imaging would be appropriate to (1) select patients who will benefit from immunotherapy; (2) discriminate between patients with a real progression of disease during immunotherapy, especially in the case of doubtful or indeterminate morphological imaging; (3) improve the definition of a clinical benefit; and (4) stratify the prognosis of patients who undergo long-term treatment with immunotherapy. However, multicentre prospective clinical trials should be appropriately drawn. Finally, although few and discordant findings are available about the prediction of response to immunotherapy in patients who will develop immune-related adverse events, the role of ^{18}F-FDG PET/CT should be addressed and further evaluated.

To obtain a national overview of the abovementioned matters of discussion, on the behalf of the Italian Association of Nuclear Medicine (AIMN), we have developed an eight-question online survey. However, an international effort should be made for providing definitive solutions to these uncertainties.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, informed consent is not required.

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