European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:1019–1021
https://doi.org/10.1007/s00259-020-04702-4

EDITORIAL

Evaluating response to immunotherapy with ^{18}F-FDG PET/CT: where do we stand?

Nicolas Aide[1,2,3] · Michel De Pontdeville[4] · Egesta Lopci[5]

Published online: 30 January 2020

In this issue of the *EJNMMI*, Seban et al. [1] propose a prognostic score combining baseline total metabolic tumor volume (TMTV) and the Derived Neutrophil-to-Lymphocyte Ratio (dLNR) to predict overall survival (OS) in non-small cell lung cancer (NSCLC) patients receiving immune-checkpoint inhibitors (ICI). In their series of 80 patients, a TMTV >75 and a dLNR >3, previously validated as a biomarker of immune activation by other groups [2], resulted as independent predictive factors for shorter OS and worse clinical benefit, the later one established according to RECIST 1.1 criteria and combining objective response (partial or complete) at any time during the course of ICI or stable disease after 6 months of treatment. The same group from Gustave Roussy Institute, had shown in melanoma patients that baseline ^{18}F-FDG PET parameters could be used to build a prognostic metabolic score using not only the TMTV but also hematopoietic tissue metabolism, namely, bone marrow to liver ratio (BLR) proving that these PET metrics had significant and independent value in predicting survival [3]. Hence, high-risk patients (high TMTV and high BLR) had worse survival compared to low-risk patients (low TMTV and low BLR). In this cohort, BLR not only outperformed spleen to liver ratio (SLR), which has been showed by others groups to predict OS in melanoma [4] but was additionally associated with transcriptomics profiles, including regulatory T cells markers.

Along with the prognostic role of the above-mentioned baseline parameters, recent data reported by another group [5] suggest a higher risk of hyper progressive disease during immunotherapy in NSCLC patients presenting with high metabolic tumor burden, expressed by both MTV and TLG, and elevated inflammatory indexes, including dNLR and platelet count. As expected, multivariate analysis identified once again MTV and dNLR as independent predictors for OS.

Of note, although tumor SUV_{max} was not found as a significant predictor of survival by Seban et al. [1], it resulted correlated to the PD-L1 expression status. This finding is in line with what previously suggested by other groups [6, 7], the hypothesis being that increased glycolytic activity can be linked to an enhanced immune infiltrate in the stromal compartment. Paradoxically, NSCLC patients presenting with a higher baseline SUV_{max} could have a higher chance of response in case of treatment with ICI. This initially theory [6] has indeed anticipated the results published only recently by Takada et al. [8] in 89 patients with advanced or recurrent NSCLC reporting a significantly higher response rate in patients with a baseline $SUV_{max} \geq 11.16$ (41.3%) compared to patients with lower SUVmax values (11.6%).

When it comes to ^{18}F-FDG PET/CT for therapy monitoring, the nuclear medicine community has been very active in the last decade, coming up with various response criteria [6, 7] including the PERCIMT (PET Response Evaluation Criteria for Immunotherapy) [9], PECRIT (PET/CT Criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy) [10], iPERCIST [11], or other PERCIST (PET Response Criteria in Solid Tumors)-adapted criteria [12]. A good example is represented by imPERCIST5 [13], developed by the Memorial Sloan-Kettering Cancer Center group in patients receiving ipilimumab. As opposed to PERCIST, where a new metastatic lesion classifies the patient as progressive metabolic disease (PMD), imPERCIST5 incorporates a new lesion

This article is part of the Topical Collection on Hematology.

✉ Nicolas Aide
aide-n@chu-caen.fr

[1] Nuclear Medicine Department, Centre Hospitalier Universitaire, Avenue Côte de Nacre, 14000 Caen, France

[2] Normandie University, Caen, France

[3] INSERM ANTICIPE, Normandie University, Caen, France

[4] Dermatology Department, Centre Hospitalier Universitaire, Caen, France

[5] Nuclear Medicine Department, Humanitas Clinical and Research Hospital, Rozzano, Italy

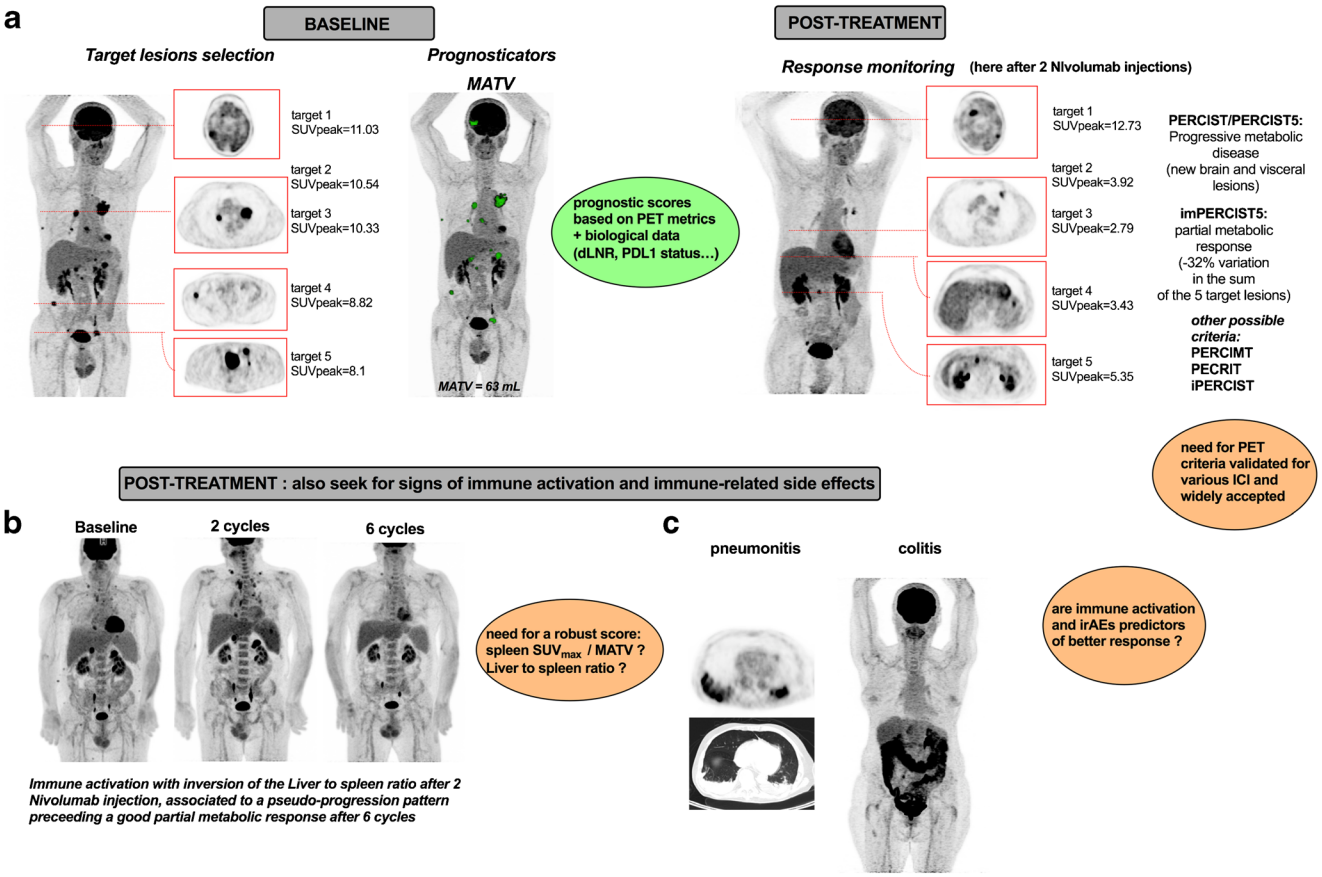

Fig. 1 Representative examples of PET metrics, response monitoring criteria (**a**) and important patterns to be sought for on follow-up scans (**b**) in patients receiving immune checkpoint inhibitors (ICI). MATV: metabolic active tumor volume; dLNR: derived lymphocytes to neutrophils ratio; PDL1: programed death ligand 1; irAEs: immune related adverse effects, PERCIST: PET Response Criteria in Solid Tumors; PECRIT: PET/CT Criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy; PERCIMT: PET Response Evaluation Criteria for Immunotherapy; ICI: immune checkpoint inhibitors

in the 5 target lesions and requires the variation in the sum of SUV_{peak} among these 5 target lesions to be greater than 30% to define disease progression. While one might argue that the rate of pseudoprogression is lower with anti PD1/PDL1 mAbs than with Ipilimumab, an anti CTLA4, these criteria could be useful in patients receiving a combination of anti CTLA4 and anti PD1/PDL1 [14], or could be tested in those patients with a progression *as per* PERCIST on early interim PET while achieving a clinical benefit. Indeed, this situation has been recently reported to occur in more than one third of the NSCLC patients treated with Nivolumab or Pembrolizumab and classified as PMD on early interim PET [15]. Description of the clinical benefit experienced by patients with atypical evolutive patterns described in the paper from Humbert and colleagues [15], along with the concept of treating patients beyond objective progression [16, 17] should probably encourage our community to a certain humility when interpreting ^{18}F-FDG PET scans until criteria are properly validated and accepted among the many PERCIST-adapted criteria proposed so far (Fig. 1a). To convince the medical oncology community, it is time to pool data and come up with user-friendly and widely adapted criteria.

Based on the recent literature, it is also obvious that the PET community should seek more than "just" tumor response [18], using baseline parameters, identification of signs of immune activation and immune-related adverse effects (irAEs) on follow-up scans (Fig. 1b). As nicely shown by Seban and colleagues, combined criteria or prognostic scores are useful when PET metrics and combined biological parameters are demonstrated to be independent prognosticators.

Compliance with ethical standards

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors. The diagnostic images herein illustrated were acquired at the Nuclear Medicine Department, University Hospital, Caen, France. Informed consent was obtained from all individual participants for the use of the clinical images.

Competing interests The authors declare no competing interest.

References

1. Seban RD, Mezquita L, Berenbaum A, Dercle L, Botticella A, Le Pechoux C, et al. Baseline metabolic tumor burden on FDG PET/CT scans predicts outcome in advanced NSCLC patients treated with immune checkpoint inhibitors. Eur J Nucl Med Mol Imaging. 2019. https://doi.org/10.1007/s00259-019-04615-x.
2. Ferrucci PF, Ascierto PA, Pigozzo J, Del Vecchio M, Maio M, Antonini Cappellini GC, et al. Baseline neutrophils and derived neutrophil-to-lymphocyte ratio: prognostic relevance in metastatic melanoma patients receiving ipilimumab. Ann Oncol. 2016;27:732–8. https://doi.org/10.1093/annonc/mdw016.
3. Seban RD, Nemer JS, Marabelle A, Yeh R, Deutsch E, Ammari S, et al. Prognostic and theranostic 18F-FDG PET biomarkers for anti-PD1 immunotherapy in metastatic melanoma: association with outcome and transcriptomics. Eur J Nucl Med Mol Imaging. 2019;46:2298–310. https://doi.org/10.1007/s00259-019-04411-7.
4. Wong ANM, McArthur GA, Hofman MS, Hicks RJ. The advantages and challenges of using FDG PET/CT for response assessment in melanoma in the era of targeted agents and immunotherapy. Eur J Nucl Med Mol Imaging. 2017;44:67–77. https://doi.org/10.1007/s00259-017-3691-7.
5. Castello A, Rossi S, Toschi L, Mazziotti E, Lopci E. Hyperprogressive Disease in Patients With Non-Small Cell Lung Cancer Treated With Checkpoint Inhibitors: The Role of (18)F-FDG PET/CT. J Nucl Med: Off Publ, Soc Nucl Med. 2019. https://doi.org/10.2967/jnumed.119.237768.
6. Lopci E, Toschi L, Grizzi F, Rahal D, Olivari L, Castino GF, et al. Correlation of metabolic information on FDG-PET with tissue expression of immune markers in patients with non-small cell lung cancer (NSCLC) who are candidates for upfront surgery. Eur J Nucl Med Mol Imaging. 2016;43:1954–61. https://doi.org/10.1007/s00259-016-3425-2.
7. Grizzi F, Castello A, Lopci E. Is it time to change our vision of tumor metabolism prior to immunotherapy? Eur J Nucl Med Mol Imaging. 2018;45:1072–5. https://doi.org/10.1007/s00259-018-3988-1.
8. Takada K, Toyokawa G, Yoneshima Y, Tanaka K, Okamoto I, Shimokawa M, et al. (18)F-FDG uptake in PET/CT is a potential predictive biomarker of response to anti-PD-1 antibody therapy in non-small cell lung cancer. Sci Rep. 2019;9:13362. https://doi.org/10.1038/s41598-019-50079-2.
9. Anwar H, Sachpekidis C, Winkler J, Kopp-Schneider A, Haberkorn U, Hassel JC, et al. Absolute number of new lesions on (18)F-FDG PET/CT is more predictive of clinical response than SUV changes in metastatic melanoma patients receiving ipilimumab. Eur J Nucl Med Mol Imaging. 2018;45:376–83. https://doi.org/10.1007/s00259-017-3870-6.
10. Cho SY, Lipson EJ, Im HJ, Rowe SP, Gonzalez EM, Blackford A, et al. Prediction of response to immune checkpoint inhibitor therapy using early-time-point (18)F-FDG PET/CT imaging in patients with advanced melanoma. J Nucl Med: Off Publ, Soc Nucl Med. 2017;58:1421–8. https://doi.org/10.2967/jnumed.116.188839.
11. Goldfarb L, Duchemann B, Chouahnia K, Zelek L, Soussan M. Monitoring anti-PD-1-based immunotherapy in non-small cell lung cancer with FDG PET: introduction of iPERCIST. EJNMMI Res. 2019;9:8. https://doi.org/10.1186/s13550-019-0473-1.
12. Aide N, Hicks RJ, Le Tourneau C, Lheureux S, Fanti S, Lopci E. FDG PET/CT for assessing tumour response to immunotherapy : report on the EANM symposium on immune modulation and recent review of the literature. Eur J Nucl Med Mol Imaging. 2019;46:238–50. https://doi.org/10.1007/s00259-018-4171-4.
13. Ito K, Teng R, Schoder H, Humm JL, Ni A, Michaud L, et al. (18)F-FDG PET/CT for monitoring of Ipilimumab therapy in patients with metastatic melanoma. Journal of nuclear medicine : official publication. Soc Nucl Med. 2019;60:335–41. https://doi.org/10.2967/jnumed.118.213652.
14. Sznol M, Ferrucci PF, Hogg D, Atkins MB, Wolter P, Guidoboni M, et al. Pooled analysis safety profile of Nivolumab and Ipilimumab combination therapy in patients with advanced melanoma. J Clin Oncol: Off J Am Soc Clin Oncol. 2017;35:3815–22. https://doi.org/10.1200/jco.2016.72.1167.
15. Humbert O, Cadour N, Paquet M, Schiappa R, Poudenx M, Chardin D, et al. (18)FDG PET/CT in the early assessment of non-small cell lung cancer response to immunotherapy: frequency and clinical significance of atypical evolutive patterns. Eur J Nucl Med Mol Imaging. 2019. https://doi.org/10.1007/s00259-019-04573-4.
16. Haddad R, Concha-Benavente F, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, et al. Nivolumab treatment beyond RECIST-defined progression in recurrent or metastatic squamous cell carcinoma of the head and neck in CheckMate 141: a subgroup analysis of a randomized phase 3 clinical trial. Cancer. 2019;125:3208–18. https://doi.org/10.1002/cncr.32190.
17. Ricciuti B, Genova C, Bassanelli M, De Giglio A, Brambilla M, Metro G, et al. Safety and Efficacy of Nivolumab in Patients With Advanced Non-small-cell Lung Cancer Treated Beyond Progression. Clin Lung Cancer. 2019;20:178–85.e2. https://doi.org/10.1016/j.cllc.2019.02.001.
18. Hicks RJ, Iravani A, Sandhu S. (18)F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography for Assessing Tumor Response to Immunotherapy in Solid Tumors: Melanoma and Beyond. PET Clin. 2020;15:11–22. https://doi.org/10.1016/j.cpet.2019.08.007.