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EDITORIAL

Therapy monitoring with PET in cancer patients: achievements, opportunities and challenges ahead for the PET community

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It has been 18 years since the first guidelines on PET response criteria were released [1] (with little supporting data at that time) and 15 years since the first successful use of PET for evaluation of a molecularly targeted therapy (imatinib) was published [2]. This latter study demonstrated the huge potential of PET imaging in assessing tumor response early after treatment initiation, at a time when conventional criteria based on size measurements (RECIST) were found to be unsatisfactorily. Since then, numerous studies using FDG PET as a surrogate marker to evaluate response to therapy have been published; PET Response Criteria In Solid Tumors (PERCIST) have been introduced [3, 4] and data regarding repeatability of PET have been published, supporting the use of thresholds to discriminate between responders and non-responders [5, 6]. Nonetheless, unfortunately, FDG PET is far from being a standard tool in clinical trials assessing new antineoplastic tools, but there have been indeed relevant progress.

It is our pleasure to introduce this special issue of the EJNMMI dedicated to therapy monitoring with PET in cancer patients, in which the reader will find up-to-date information on the basis of tumor biology and new PET technologies for therapy assessment with FDG and other PET probes in solid tumors and in hematological tumors.

We have divided the issue into four sections. The first section includes a recent update on PET technologies and two articles discussing the motivations and methodology for harmonization of PET data and the challenges faced when implementing PET in clinical trials. It is followed by a section including a practical guide to better understand molecularly targeted therapies, and a comprehensive review on the use of the EORTC PET response criteria as well as the PERCIST. The third section reviews therapy monitoring with ^{18}F-FDG, ^{18}F- or ^{11}C-Choline, ^{68}Ga-PSMA and Sodium Fluoride in solid tumors, while the fourth and last section reviews therapy monitoring in hematological malignancies.

One might consider that the natural history of PET technologies and antineoplastic drugs is somewhat similar, both being characterized by continuous improvements and from time to time a major breakthrough. In this EJNMMI special issue, Van der Vos et al. [7] review hardware (digital PET) and software (advanced reconstruction algorithms) PET technological improvements, digital PET being expected as a major breakthrough by the PET community. While these advances give our community great opportunities such as a better staging capability thanks to an improvement in small lesions detectability, they also bring challenges in getting harmonized images/quantitative values in PET centers running different PET systems and in multicentre clinical trials, as reviewed by Aide et al. [8] in a paper also discussing the EANM response to this issue, namely the EARL accreditation program. Yet, harmonization of PET data is only one of the problems faced by the medical oncology and PET communities when trying to implement PET with FDG or other probes as biomarkers in multicentre clinical trials, as discussed by Deroose and colleagues from the EORTC imaging group in a paper covering all the challenges faced in this setting [9].

The EJNMMI readers will then find a guide to better understand the biological bases of the main categories of

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antineoplastic drugs [10], with a focus on immunotherapy with anti-PD1 and anti-PDL1 checkpoint inhibitors. This new therapy can be considered as a major breakthrough in oncology, but it also raises the issue of pseudo-progression: such event may occur early in the course of treatment with anti-PD1/PDL1 checkpoints, and was first described with CT, being defined as a transient increase in tumor burden including the potential appearances of new lesions. Radiologists tried to overcome the problem by using dedicated CT criteria, the irRC [11]; a challenge for the PET community will certainly be to find a solution to this issue, maybe by upgrading (like the recent update of the Lugano classification in lymphoma [12]) the existing EORTC criteria and PERCIST, which are compared in detail by Pinker et al. [13].

In line with the previous section, the third section includes a review from Wong et al. [14] in melanoma, one of the first tumor types to have proven benefits from immunotherapy treatments. This review from Australian colleagues discusses in particular the problematic pseudo progression following treatment initiation and describes not only how immune-related side effects can be identified on PET, but also reviews in detail PET monitoring of other molecularly targeted therapies. With published studies involving several hundred patients, the efficiency of Choline [15] and more recently PSMA [16] PET has been proven in detecting prostate cancer relapse, while robust data on the use of such tracers to evaluate response to therapy are still lacking. Ceci et al. [17] discuss the use of PET for therapy monitoring in castration resistant prostate cancer. Of note, the success of nuclear medicine in prostate cancer is based not only on its diagnostic capabilities, but also on achieving a gain in overall survival as well as improvement of quality of life in bone-metastatic refractory prostate cancer patients treated with Radium^{223} [18, 19]. Etchebehere et al. [20] review the use of Sodium Fluoride PET in this setting, using this probe for baseline tumor burden assessment and to monitor the effect of radium^{223}.

The fourth section is dedicated to hematological malignancies. The use of PET in Hodgkin and non-Hodgkin lymphoma patients is definitely to be counted in the achievements of our community. Yet, as always there is room for improvement, a good example being the quantitative extension of the Deauville scale (DS) to better characterize those patients with a residual disease harboring an FDG uptake greater than the liver (DS 4 and 5), as discussed by Barrington et al. [21]. Also addressed in this section is the use of PET in myeloma, with a paper from Nanni et al. [22] detailing, in particular, techniques to better assess the whole body tumor burden.

We trust this EJNMMI issue will be of interest to the Nuclear Medicine and Medical Oncology communities, and we would like to thank the authors for their contributions and Prof. Ignasi Carrio for his support in his capacity as the Editor-in-Chief of the EJNMMI.

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