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LETTER TO THE EDITOR

^{18}F-FDG PET/CT in multiple myeloma: critical insights and future directions

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Sir,

We read with interest the articles by Jung et al. [1] and Ripani et al. [2] recently published in this journal. These studies point out the prognostic impact of ^{18}F-FDG PET/CT at diagnosis and for therapy assessment in patients with multiple myeloma (MM). They are also the most recent in a wave of published articles which particularly highlight the increased attention received by this imaging technique in this pathology over the last decade. However, we believe it necessary to draw the attention of readers who might be swept along by this prevailing view to the urgent need for standardization to enable the field to move forward. Consistent with previous experience in lymphomas, ensuring reproducibility by establishing clear guidelines [3] is warranted before ^{18}F-FDG PET/CT can be used in everyday routine in MM patients, and such guidelines need to be fully endorsed by the haematology community. The main risk with this flow of publications is that we are drowned in the multitude of heterogeneous imaging analysis criteria. We address here some key points on existing recommendations and perspectives.

Recently, the International Myeloma Working Group (IMWG) has fully incorporated ^{18}F-FDG PET/CT into the diagnosis and staging of MM [4] regarding bone disease. The presence of osteolytic lesions is a hallmark of MM and is independent of the presence or absence of FDG uptake. Several studies have shown the usefulness of ^{18}F-FDG PET/CT for the detection of MM lesions with a sensitivity and specificity varying from 80% to 100% [5]. Indeed, the CT portion of the PET/CT evaluation provides high-resolution bone imaging that allows a higher rate of detection of lytic bone disease than that achieved with skeletal survey in earlier phases. The ability of ^{18}F-FDG PET/CT to depict metabolic activity is only secondary, but provides powerful and reliable prognostic information. Although no standard criteria have been validated so far, abnormalities detected by ^{18}F-FDG PET/CT in MM are mostly classified into four categories: (1) focal lesions (FL), defined as lesions with ^{18}F-FDG uptake higher than that of the bone marrow or the liver background; (2) paramedullary lesions (PML), defined as FL with contiguous soft tissue involvement; (3) diffuse medullary involvement, defined as diffuse bone uptake greater than that of the liver; and (4) extramedullary disease (EMD).

Since the initial work by the Little Rock group almost 10 years ago, the presence of more than three FDG-avid FLs has been known to be associated with poorer survival in MM patients [6]. This has since been confirmed by more than one independent study, as has the negative prognostic value of EMD [7–10]. Indeed, these two prognostic factors provide two major pieces of information: the number of FLs possibly reflects spatial genomic heterogeneity [11], and EMD is a highly aggressive disease entity and is different from marrow-restricted myeloma [12, 13]. In their recent work, Jung et al. [1] similarly found that patients with more than three FLs or EMD had significantly poorer survival. Jung et al. also explored the combination of these two entities as a single factor (so-called "PET/CT-positive"). The combination of these data extracted from ^{18}F-FDG PET/CT clearly identified a subset of patients with a higher risk of progression who might benefit from more intensive therapy, but the term used seems inappropriate. The definition of "PET/CT-positivity" is indeed given by the IMWG recommendations as the presence

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of at least one FL that defines a "bone lesion" in the CRAB criteria [4]. The term "PET/CT prognostic index" is perhaps more appropriate than "PET/CT-positive". Whilst this study was a retrospective analysis performed in patients receiving different therapeutic programmes, it does highlight the potential added value of integrating ^{18}F-FDG PET and known prognostic factors in the management of MM for therapy decision making. Future studies should point in this direction.

^{18}F-FDG PET/CT is also a reliable tool for therapy assessment in MM. Obtaining complete metabolic remission (CMR) on ^{18}F-FDG PET/CT in an intermediate evaluation before or after autologous stem-cell transplantation (ASCT) is associated with a better survival rate, especially in patients with a complete biological response [8, 14–16]. On the other hand, follow-up MRI performed after therapy is usually less satisfactory due to a high frequency of false-positive images [17]. For these reasons, the IMWG strongly recommends that ^{18}F-FDG PET/CT be considered as the preferred imaging technique to evaluate response to therapy in MM [4, 14], and a new definition of response including PET has been proposed by international experts [14]. Despite promising results reported by different groups, the lack of standard interpretation criteria again makes it difficult to provide general guidelines. In several studies image interpretation was based mainly on semiquantitative analysis, and in others on visual assessment or on both methods.

In the French IMAJEM study [8], CMR was considered equivalent to the absence of residual diffuse bone uptake, and FL and EMD as uptake above hepatic uptake, while Bartel et al. [6] and Zamagni et al. [7] used surrounding normal tissue as background. In this context, the Italian myeloma criteria for PET use (IMPeTUs) drafted by a group of Italian nuclear medicine experts appears to be a useful framework [18]. Nevertheless, these criteria are still somewhat complicated, as a lower concordance rate was found between readers after therapy [19]. However, in these studies, liver background, equivalent to the threshold in lymphomas used with the Deauville scale, stands out as an effective cut-off to distinguish between active and inactive disease. The ongoing CASSIOPET prospective study (ClinicalTrials.gov identifier NCT02541383; https://clinicaltrials.gov) that aims to determine the best CMR cut-off for positivity on ^{18}F-FDG PET/CT might provide some guidance on the matter.

In parallel, as demonstrated for lymphoma [3, 20], quantitative measures such as maximal standardized uptake value (SUV) are an attractive option. For example, in patients with FDG-avid MM included in the IMAJEM cohort, ΔSUVmax after three cycles of chemotherapy identified patients with improved median progression-free survival ($p < 0.001$) [21]. Ripani et al. reported apparently similar results with the use of SUV values normalized to liver uptake [2]. Although this second report of normalization of SUVmax in MM is a first important step in image analysis, the generalization of its conclusion is limited by important biases. First, changes in SUVmax were expressed as absolute values rather than as percentage changes between the pretreatment and posttreatment ^{18}F-FDG PET/CT scans. As acknowledged by the authors, the study was conducted on three different PET/CT systems which could have significantly impacted their conclusion when dealing with absolute changes in SUVmax [22]. Besides, the studied population included both patients with untreated MM and patients with relapsing MM resulting in a possible confounding effect since recurrent disease is usually more aggressive on presentation due to the selection of resistant clones. Moreover, the authors did not distinguish between patients with low and high uptake at baseline, resulting in a possible additional bias when the baseline SUVmax was too low for posttreatment changes to be reliably differentiated from variability. Nevertheless, this approach has merit and warrants further study to validate this important observation.

Keeping in mind these limitations, further efforts by a joint French/Italian consortium are ongoing [23]. This task force aims to harmonize the interpretation criteria for ^{18}F-FDG PET/CT at baseline and for response assessment based on existing criteria developed by these two cooperative groups (the Cassio PET criteria from the French group and the IMPetUS criteria from the Italian group) and on a combined analysis of prospective trials. Preliminary results were recently presented at the 60th annual meeting of the American Society of Hematology [24].

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval This article does not describe any studies with human participants performed by any of the authors.

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