Review

Positron Emission Tomography (PET) Imaging of Multiple Myeloma in a Post-Treatment Setting

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Abstract: 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission tomography/computed tomography (FDG PET/CT) has an established clinical value in the diagnosis and initial staging of multiple myeloma (MM). In the last ten years, a vast body of literature has shown that this tool can also be of high relevance for monitoring therapy responses, making it the recommended imaging approach in this field. Starting from the strengths and weaknesses of radiological imaging in MM, the present review aims to analyze FDG PET/CT’s current clinical value focusing on therapy response assessment and objective interpretation criteria for therapy monitoring. Given the potential occurrence of patients with MM showing non-FDG-avid bone disease, new opportunities can be provided by non-FDG PET tracers. Accordingly, the potential role of non-FDG PET tracers in this setting has also been discussed.

Keywords: multiple myeloma; positron emission tomography; magnetic resonance imaging; response assessment

1. Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and is associated with the abnormal proliferation of well-differentiated plasma cells [1]. This condition is eventually preceded by an asymptomatic phase (the monoclonal gammopathy of undetermined significance, MGUS), characterized by increased clonal plasma cell levels in the bone marrow without organ involvement [1]. In some cases, an intermediate phase, defined as smoldering multiple myeloma (SMM) is also described [2]. Patients with active MM show a high serum free light chain ratio and plasma cell content in the bone marrow (>60%) [3]. The evolution from MGUS/SMM to active MM is also associated with the appearance of clinical signs of organ damage including renal insufficiency, hypercalcemia and anemia as well as the presence of bone involvement documented by radiological imaging.

For this reason, imaging technologies have become crucial in many phases of the disease. In particular, low dose computed tomography (CT) and magnetic resonance imaging (MRI) allow the early recognition of osteolytic lesions and the assessment of the bone marrow involvement, respectively. This anatomical description provides relevant information in the earlier phases of the disease. On the other hand, in the last years, a vast body of literature has demonstrated the added value of 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography/computed tomography (FDG PET/CT) over standard imaging in many phases of the disease including the initial diagnosis and staging [3–8], restaging at
relapse [9–11], prognostic assessment [9,12–15] and monitoring therapy response. This latter indication has been increasingly studied due to the emerging capability of FDG imaging to detect with high sensitivity the persistence of residual active clonal plasma cells within residual lytic lesions, which are of adverse prognostic significance [16]. Moreover, FDG PET/CT is superior to MRI in the early detection of a response to salvage therapy [17]. These findings supported FDG imaging inclusion in the consensus recommendations by the International Myeloma Working Group (IMWG) [3,18].

On these bases, starting from the strengths and weaknesses of radiological imaging in MM, the present review aims to analyze the current state of the art of FDG PET/CT focusing on the post-treatment setting with a particular interest in the therapy response assessment. Given the potential occurrence of patients with MM showing non-FDG-avid bone disease, new opportunities can be provided by non-FDG PET tracers. Accordingly, the potential role of non-FDG PET tracers in this setting has also been discussed.

2. Methods

Aiming to systematically review the available literature on the FDG PET/CT-based response assessment in MM, we combined the following terms (either as text or MeSH) in PubMed, PMC, Scopus, Google Scholar, Embase, Web of Science and the Cochrane library: “multiple myeloma”, “Positron Emission Tomography”, “Fluorodeoxyglucose”, “Response”, “therapy” and “treatment”. The literature analysis was lastly updated in November 2020. No language restriction was applied to the search but only articles in English were reviewed. Similarly, preclinical studies, case reports and case series involving less than five patients were excluded. The systematic literature search returned 375 articles, which were analyzed according to the title and abstract. After the removal of duplicates, 29 articles were considered and fully read (Table 1). This approach led to the exclusion of 346 articles. Aiming to contextualize the above-mentioned topic, a further literature search focusing on the remaining clinical applications of FDG PET/CT in MM, on the complementary role of MRI and on non-FDG PET tracers was also performed through the same databases. Due to the extensive existing literature about these topics, these articles were not systematically reviewed. Therefore, the corresponding sections represent a narrative description of the clinical background for FDG PET/CT imaging therapy monitoring in this field.
Table 1. Available studies on FDG PET/CT in therapy monitoring multiple myeloma.

| Ref   | First Author, Year | Country     | Number of Patients | Population       | Study Design | Administered Therapy | Timepoint | Follow-Up Duration | Images Evaluation | Endpoint/Gold Standard | Major Findings                                                                                   |
|-------|--------------------|-------------|--------------------|------------------|--------------|----------------------|-----------|--------------------|----------------------|----------------------------|-----------------------------------------------------------------------------------------------|
| [19]  | Jadvar, H., 2002   | USA         | 6                  | MM               | PCS          | CTx + auto-BMT        | Baseline and 3 months after therapy | n.a.            | Qualitative          | CO                   | Clinical outcome following treatment administration is paralleled by FDG uptake changes. FDG PET allows the evaluation of the presence of ongoing disease activity in previously irradiated sites remaining abnormal at skeletal imaging after treatment. FDG PET was helpful in describing post-therapeutic changes. However, there was one false-positive FDG PET result in a patient who had undergone RT three weeks before PET. |
| [20]  | Mileshkin, L., 2004| Australia   | 69                 | MM               | RS           | RT                   | Baseline | n.a.            | Qualitative          | n.a.                       | FDG PET allows the evaluation of the presence of ongoing disease activity in previously irradiated sites remaining abnormal at skeletal imaging after treatment. |
| [5]   | Bredella, M.A., 2005| USA         | 9/13               | MM               | RS           | CTx, RT, surgery, or BMT | Baseline and 3 months after therapy | n.a.            | Qualitative, semiquantitative (SUVmax, SUVmean) | CO                   | FDG PET was helpful in describing post-therapeutic changes. However, there was one false-positive FDG PET result in a patient who had undergone RT three weeks before PET. |
| [6]   | Zamagni, E., 2007  | Italy       | 23/46              | MM               | PCS          | Auto-BMT             | Baseline and 3 months after therapy | n.a.            | Qualitative, semiquantitative (SUVmax) | M protein concentration, MRI, CO | Restaging PET scans after RT successfully assessed the response to treatment in all. Of note, two patients showed late responses. |
| [21]  | Kim, P.J., 2008    | USA, Australia| 11/17              | Plasmacytoma     | RS           | RT                   | Baseline, before each BMT, before consolidation and maintenance and semiannually thereafter | 4-96 months | Qualitative, semiquantitative (SUVmax) | CO                   | MM survival can be improved by altering treatment in patients in whom FDG suppression is not achieved after induction CTx. |
| [16]  | Bartel, T.B., 2009 | USA         | 239                | MM               | PCS          | Total Therapy 3 scheme [22] | Baseline and 2–4 weeks after therapy Baseline, before each BMT, before consolidation and maintenance and semiannually thereafter | 43 months (median) | Qualitative, semiquantitative (SUVmax) | PFS and OS | Early FDG kinetics studies (after 1 cycle of CTx) successfully predict the subsequent PFS in MM. |
| [22]  | Dimitrakopoulou-Strauss, A., 2009 | Germany | 19                | MM               | PCS          | CTx                  | Baseline and 2–5 weeks after therapy | 0–64.1 months | Qualitative, semiquantitative and dynamic imaging parameters calculated according to Patlak model | PFS | FDG PET allows the evaluation of the presence of ongoing disease activity in previously irradiated sites remaining abnormal at skeletal imaging after treatment. |
| [24]  | Sager, S., 2011    | Turkey      | 10/42              | MM, plasmacytoma | RS           | n.a.                 | Baseline and 3 weeks after therapy | At least 6 months | Qualitative, semiquantitative (SUV) | CO | FDG PET allows the evaluation of the presence of ongoing disease activity in previously irradiated sites remaining abnormal at skeletal imaging after treatment. |
Table 1. Cont.

| Ref | First Author, Year | Country | Number of Patients | Population | Study Design | Administered Therapy | Timepoint | Follow-Up Duration | Images Evaluation | Endpoint/Gold Standard | Major Findings |
|-----|---------------------|---------|--------------------|------------|-------------|----------------------|-----------|--------------------|---------------------|----------------------|-----------------|
| [12] | Zamagni, E., 2011 | Italy | 192 | MM | PCS | Induction CTx and double auto-BMT | Baseline, within 10 days after induction therapy, 3 months after auto-BMT, during follow-up and at the time of relapse post-BMT setting (median interval 33.9 ± 31.5 months, range 1.2–143.1) post-BMT setting (median interval 37.4 ± 38.1 months, range 2.4–143.1). Baseline, after 3 months from BMT and every 6–12 months during follow-up | 42 months (median) | Qualitative, semiquantitative (SUVmax) | PFS and OS | The persistence of hypermetabolic lesions after induction CTx is an early predictor for shorter PFS. Three months after auto-BMT, a negative FDG PET/CT is associated with a more favorable 4-year rate of PFS and OS with respect to PET-positive |
| [11] | Derlin, T., 2012 | Germany | 99 | MM | RS | Auto or allo-BMT | Baseline, after 6 months from BMT and every 12 months in the follow-up | n.a. | Qualitative, semiquantitative (SUVmax) | CO | Post-BMT FDG PET/CT contributes to the restaging but has a substantially lower sensitivity for this purpose compared with the pretreatment setting |
| [25] | Derlin, T., 2013 | Germany | 31 | MM | RS | Autologous or allogenic BMT | Baseline, after 3 months from the first line of therapy and every 12–18 months during post-treatment follow-up | 6 months (range 1–122) | Qualitative, semiquantitative (SUVmax) | PFS, OS | PET/CT is more accurate than MRI for the determination of the remission status after BMT |
| [26] | Nanni, C., 2013 | Italy | 107 | MM | PCS | Auto-BMT | Baseline, at day 7 from induction and before the first BMT. Baseline, after 6 months from BMT and every 6–12 months during follow-up. Baseline, after 3 months from the first line of therapy and every 12–18 months during post-treatment follow-up | 41 months (mean) | Qualitative, semiquantitative (SUVmax) | DFS, TTR | In the post-BMT setting, a negative FDG PET/CT predicts favorable DFS and TTR while metabolically active disease persistency is correlated with shorter TTR |
| [27] | Usmani, S.Z., 2013 | USA | 302 | MM | PCS | Total Therapy 3 scheme [22] | Baseline, after 6 months from BMT and every 12 months in the follow-up. Baseline, after 3 months from the first line of therapy and every 12–18 months during post-treatment follow-up | 6.8 years (TTR 3A) and 4.3 years (TTR 3B) | Qualitative, semiquantitative (SUVmax) | CRD, PFS, OS | The presence of more than 3 PET focal lesions after day 7 first cycle of induction CTx predicts inferior PFS and OS. The persistence of extramedullary disease and a failure to obtain a metabolic response after allo-BMT are associated with shorter PFS and OS |
| [28] | Patriarca, F., 2015 | Italy | 59/67 | MM | RS | Allo-BMT | Baseline, after 6 months from BMT and every 12 months in the follow-up. Baseline, after 3 months from the first line of therapy and every 12–18 months during post-treatment follow-up | 67 months (median) | Qualitative, semiquantitative (SUVmax) | PFS, OS | The failure to achieve a complete metabolic response after the first-line treatment predicts lower PFS and OS |
| [15] | Zamagni, E., 2015 | Italy | 282 | MM | RS | CTx and/or BMT | Baseline, after BMT | 16.63 months (range 4.97–33.33) | Qualitative, semiquantitative (SUVmax, T/Mmax) | DFS, OS | T/Mmax overcomes SUVmax for the evaluation of the treatment response |
| [29] | Li, Y., 2017 | China | 67/98 | MM | PCS | CTx and BMT | Baseline, after BMT | 16.63 months (range 4.97–33.33) | Qualitative, semiquantitative (SUVmax, T/Mmax) | DFS, OS | T/Mmax overcomes SUVmax for the evaluation of the treatment response |
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| Ref | First Author, Year | Country | Number of Patients | Population | Study Design | Administered Therapy | Timepoint | Follow-Up Duration | Images Evaluation | Endpoint/Gold Standard | Major Findings |
|-----|------------------|---------|-------------------|------------|--------------|-------------------|-----------|--------------------|-------------------|------------------------|----------------|
| [30] | Nanni, C., 2016  | Italy   | 17                | MM         | PCS          | CTx and BMT       | Baseline, after induction, end of therapy | n.a.          | Qualitative, semiquantitative (SUVmax), IMPetUs criteria Qualitative, semiquantitative (SUVmax), quantitative | n.a. | Response assessment by means of IMPetUs criteria is feasible in the clinical practice |
| [31] | Sachpekidis, C., 2017 | Germany | 29/34             | MM         | PCS          | CTx and BMT       | Baseline, after 3 months from therapy | 15-52 months | n.a. | PFS, OS | 18F-NaF PET/CT does not add significantly to 18F-FDG PET/CT in the treatment response evaluation of MM |
| [32] | Moreau, P., 2017  | France  | 134               | MM         | PCS          | CTx +/- BMT       | Baseline, after three cycles of CTx and before maintenance | 30 months | Qualitative, semiquantitative (SUVmax), quantitative | PFS, OS | FDG PET/CT normalization before maintenance is associated with better PFS and OS |
| [33] | Stolzenburg, A., 2018 | Germany, USA | 52               | MM         | RS           | Allo-BMT          | Before and after BMT (91 ± 50 days after) | 62.3 months (range 29-124) | Qualitative, semiquantitative (SUVmax) | PFS, OS | FDG PET/CT negativity prior to or following allo-BMT is a favorable prognostic factor for PFS and OS |
| [34] | Bassa, M.A., 2018 | Egypt   | 22/56             | MM         | PCS          | CTx, RT or BMT    | Baseline, after 6 months from therapy | 9 months | Qualitative, semiquantitative (SUVmax), Qualitative, semiquantitative (SUVmax), IMPetUs criteria | CO, bone marrow biopsy | |
| [35] | Nanni, C., 2018   | Italy   | 86                | MM         | PCS          | CTx and BMT       | Baseline, after induction, end of therapy | n.a.          | Qualitative, semiquantitative (SUVmax), IMPetUs criteria Qualitative, semiquantitative (SUVmax), IMPetUs criteria | n.a. | Response assessment by means of IMPetUs criteria is highly reproducible in the clinical practice |
| [22] | Zamagni, E., 2018 | International multicentric | 236 | MM | PCS | CTx and BMT | Baseline, prior to the start of maintenance | 62.9 months (median) | Qualitative, semiquantitative (SUVmax), IMPetUs criteria Qualitative, semiquantitative (SUVmax), IMPetUs criteria | PFS, OS | Reduction of the focal lesion and bone marrow FDG uptake to a lower degree than the liver after therapy independently predicts PFS and OS |
| [36] | Bailly, C., 2018  | France  | 71                | MM         | PCS          | CTx               | Baseline and after three cycles of CTx | 21.5 months (median) | Qualitative, semiquantitative (SUVmax), IMPetUs criteria Qualitative, semiquantitative (SUVmax), IMPetUs criteria | BR, PFS | Early FDG PET/CT response assessment (interim) predicts the long-term CO |
| [37] | Ripani, D., 2019  | Italy   | 28                | MM         | RS           | CTx and BMT       | Baseline and 4.8 ± 1.5 months after treatment completion | 48.2 ± 9.8 months (mean) | Qualitative, semiquantitative (SUVmax, SUVmean, MTVsum, TLGsum, rPET, qPET) Qualitative, semiquantitative (SUVmax, SUVpeak, SUVmean) | TMP | Semiquantitative normalized FDG PET-CT parameters outperform non-normalized indexes in the prediction of persistent response to treatment |
| [38] | Nakuz, T.S., 2019 | Austria | 7                 | MM         | PCS          | CTx, RT, BMT      | Baseline, at 10 and 17 months from therapy beginning | 45 months (median) | Qualitative, semiquantitative (SUVmax, SUVpeak, SUVmean) | BR | FDG PET/CT overcomes NaF PET/CT in the description of persistent treatment-related metabolic changes |
Table 1. Cont.

| Ref | First Author, Year | Country | Number of Patients | Population | Study Design | Administered Therapy | Timepoint | Follow-Up Duration | Images Evaluation | Endpoint/Gold Standard | Major Findings |
|-----|-------------------|---------|--------------------|------------|--------------|----------------------|-----------|-------------------|----------------------|----------------------|-----------------|
| [39] | Zamagni, E., 2020 | International multicentric | 228 | MM | PCS | CTx +/− BMT | Baseline, after induction CTx, before maintenance: Baseline, after treatment (median 102 days after) | 62.9 months (median) | Qualitative, semi-quantitative (SUVmax), IMPeTUs criteria Qualitative, semi-quantitative (SUVmax), IMPeTUs criteria | PFS, OS | After therapy focal lesions and bone marrow FDG uptake lower than the liver background independently predicts PFS and OS DWI-MRI and ADC correlates with FDG PET/CT and the IMWG response criteria Dual time point (1 and 3 h post-injection) FDG PET/CT imaging may improve the treatment response assessment |
| [40] | Paternain, A., 2020 | Spain | 27 | MM | PCS | CTx +/− BMT | Baseline, after treatment (median 102 days after) | n.a. | Qualitative, semi-quantitative (SUVmax), IMPeTUs criteria IMWG response criteria | IMWG response criteria | DWI-MRI and ADC correlates with FDG PET/CT and the IMWG response criteria |
| [41] | Zirakchian Zadeh, M., 2020 | USA | 36 | MM | PCS | CTx +/− auto-BMT | At baseline and after therapy | n.a. | Semi-quantitative: global SUVmean (GSUVmean) | IMWG response criteria | Dual time point (1 and 3 h post-injection) FDG PET/CT imaging may improve the treatment response assessment |

ADC: Apparent Diffusion Coefficient; BMT: Bone marrow transplant; BR: Biochemical response; CO: Clinical Outcome; CRD: Complete response duration; CTx: Chemotherapy; DFS: Disease-free survival; DWI: Diffusion weighted imaging; IMWG: International Myeloma Working Group; MM: Multiple myeloma; MRI: Magnetic resonance imaging; MTV: Metabolic Tumor Volume; OS: Overall Survival; PCS: Prospective; PFS: Progression Free Survival; qPET: Lesion SUVpeak/liver SUVmean; rPET: Lesion SUVmax/liver SUVmax; RS: Retrospective; RT: Radiotherapy; SUV: Standardized Uptake Value; T/Mmax: Ratio of SUVmax in lesions to SUVmax in the mediastinum; TLG: Total Lesion Glycolysis; T/M: Time to Metabolic Progression; TTR: Time to Relapse.
3. Value and Limits of MRI in Multiple Myeloma in the Post-Treatment Setting

Since 2014, the IMWG has included MRI instead of standard radiography in the MM diagnostic criteria [3,18]. Thanks to its high sensitivity and the absence of radiation exposure, this tool can be used for diagnostic and prognostic purposes in various phases of the disease [42,43]. However, due to its functional nature, besides the mere anatomic description of the MM-related bone subversion, MRI can also evaluate the response of therapy. Through the injection of a gadolinium-based contrast medium, it allows the estimation of neoangiogenesis. The resulting time-intensity curve temporal variation can be quantitatively analyzed, allowing the measurement of the decrease in MM perfusion [44], which correlates with a biochemical response [45,46]. Similarly, the quantification of active tumor load as displayed by diffusion weighted sequences (DWI, which represent the diffusion of water molecules) appears to differentiate between treatment responders and non-responders [47,48], allowing the prediction of response to induction and consolidation chemotherapy [49]. Finally, MRI can display the occurrence of several treatment-related side effects including the osteonecrosis of the femoral head (Figure 1).

However, since the role of MRI in MM is still expanding, several further functional data can be added to the standard morphological parameters. This rapidly evolving scenario implies the extreme variability in the choice of imaging protocols and the use of contrast agents by the available studies, representing the current major limitation of this tool in the post-treatment setting [50,51]. On these bases, several efforts have been dedicated to the standardization and the decrease of variations in the acquisition, interpretation and reporting of MRI, allowing better response assessments that has led to the Myeloma Re-

![Figure 1. An emblematic case of bilateral femoral head osteonecrosis in a post-transplanted multiple myeloma (MM) patient. In the femoral head osteonecrosis is a double line sign with a low signal intensity and outer rim and high signal intensity inner line as demonstrated on the coronal T2-weighted image.](image-url)
response Assessment and Diagnosis System (MY-RADS) [50]. MY-RADS criteria are designed to provide a comprehensive characterization of the myeloma state at diagnosis, at the start of treatment, after therapy and during follow-up. However, it requires validation within clinical trials including assessments of reproducibility, correlations with the biochemical response, skeletal events, progression-free survival (PFS) and overall survival (OS).

A further matter of debate is the adequate timing of MRI imaging in the post-treatment setting. Indeed, a decrease in the apparent diffusion coefficient (ADC) following therapy can be considered an indirect index of response as it indicates the degree of water movement within extracellular and intracellular space (proxies of tissue cell density), which typically decreases during the transition from active disease to remission [51]. However, the direction of the ADC change can be profoundly influenced by imaging timing. Messiou et al. showed a transient increase in ADC values soon after therapy, presumably related to plasma cell death and the resulting increased extracellular space [51]. Therefore, to improve the appropriateness of MRI image interpretations, it should always coincide with clinical routines where serum and marrow assessments are performed [50].

4. FDG PET/CT Images Interpretation in Therapy Monitoring of Multiple Myeloma

The functional nature of FDG imaging may also allow the assessment of treatment response in MM. Indeed, while morphologic changes of lytic lesions remain relatively stable in time (scarcely displaying treatment efficacy), metabolic changes related to treatment occur in a relatively short time and can be easily measured and monitored.

Regarding metabolic activity, MM includes a heterogeneous spectrum ranging from low to extremely high FDG-avid disease [52,53]. Consequently, both false-positive and negative results may occur when monitoring the FDG imaging response in MM [53]. Sources of false-positive results include many conditions such as inflammation, recent bone fractures, post-surgical or vertebroplasty sites, bone remodeling, the presence of orthopedic devices with consequent significant artifacts on CT images, infection, diffuse bone marrow uptake such as under specific treatments (chemotherapy, radiotherapy, use of growth factors) or in other clinical states associated with a hot background in the bone (i.e., an anemic condition or the administration of erythropoietin) [16]. On the other hand, PET sensibility can be hampered by elevated glycemic levels, high-dose steroid therapy, low hexokinase-2 expression [52,53] or the presence of pure lytic lesions characterized by a low FDG uptake or an early PET-positive lesion without a correspondent osteolytic area. Furthermore, the spatial resolution of PET imaging could be insufficient to detect the typical salt and pepper Bone Marrow (BM) infiltration or to identify the occurrence of small lytic lesions in specific anatomic districts (such as the skull with the close brain physiological activity), generating possible misinterpretations [54].

The identification of standardized imaging criteria is thus of pivotal importance to estimate MM’s extent and metabolic activity in the everyday clinical use of FDG PET/CT, particularly in the post-treatment setting. On these bases, in the last years several studies have tried to identify clinically valuable PET derived indexes and to harmonize PET scan interpretation, thus overcoming the limited reproducibility of the several previous clinical trials in different clinical settings [16,32,54]. During PET reporting, image interpretation is generally based on a pure visual assessment, semiquantification or both methods.

The visual inspection of FDG PET/CT images remains undoubtedly the first step because it is free from technical artifacts and allows the harmonization of PET reporting [55]. Nevertheless, Standardized Uptake Value (SUV) calculation allows a more standardized estimation of metabolic activity particularly in the response assessment to therapy. Within the same PET center, the measure of SUV can thus eliminate inter-observer variations. However, when a given semiquantitative positivity cut-off is set, different image reconstruction algorithms could be adopted for the different scanners. This discrepancy, especially in the absence of international scanner calibration, contributes to an increase in SUVmax variability, hampering image interpretation and worsening the reproducibility of the results particularly in borderlines cases. For these reasons, a few studies have proposed using this
parameter in relation to a background reference region such as physiologic bone marrow uptake in lumbar vertebrae, a mediastinal blood pool or physiological liver uptake [55]. Aside from the use of normalized semiquantitative indexes, additional PET derived volumetric parameters such as the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been proposed as well. A few studies have analyzed the variation of these parameters after therapy as an index of treatment response [9,56].

After the initial tentative research by Mesguich et al. [57], who proposed a series of general indications for FDG PET/CT interpretation in patients with MM at different stages of the disease, an Italian group proposed visual descriptive criteria termed Italian Myeloma Criteria for PET Use (IMPeTUs) [30], specifically dedicated to the evaluation of the end of therapy PET compared with the baseline. These criteria were derived from the Deauville criteria used for the FDG-PET response assessment in Hodgkin lymphoma [58]. Furthermore, even if they were aware of the limitations derived from the use of different PET scanners with a consequent variation in SUV measurement, the authors also considered a semiquantitative analysis (lesion-to-background SUV ratio) in case of equivocal results. Despite a lower concordance in the recognition of skull lesions and of lesions still active after therapy as common pitfalls in MM, they obtained good results in terms of reproducibility among reviewers, at least in a cohort of 22 patients. These results were subsequently reproduced by the same group in a larger cohort [35]. Of note, when enlarging the sample size, a higher agreement was reached for lesions with a score 4 involving bone marrow and soft tissues in the post-therapy assessment.

IMPeTUs descriptive criteria proved to be highly reproducible, relatively easily applicable in clinical practice and recognized as the first step towards the harmonization of PET interpretation in MM patients. However, the complementary role of PET and morphological imaging is another aspect that must be considered in imaging reporting and it is even more relevant in the post-therapy setting in which functional changes usually precede morphological ones. Accordingly, IMPeTUs criteria require the reporting of the degree of the bone marrow involvement by MM and the inclusion of a number of additional characteristics of the disease to provide a complete picture of the pathological involvement. These further data include the number and site of hypermetabolic foci, the coexistence of lytic lesions and the presence of extra or para-medullary involvement as well as the presence of fractures.

As a further source of validation, IMPeTUs criteria were also used to define a posteriori positivity cut-off using patients’ follow-up data in a large population to identify subjects with active disease, especially in the post-therapy setting. In particular, the presence of a score ≥4 in the bone with either a focal or a diffuse pattern predicted a worse outcome [22].

The strength of these criteria was also confirmed in recent work by Shengming et al. [59]. IMPeTUs resulted in being significantly more accurate concerning the Durie–Salmon and the Revised International classification systems. Indeed, a profound knowledge of MM’s aspects allows a better comprehension of which imaging finding must be underlined for its clinical relevance or its prognostic impact, which instead is collateral or intrinsically equivocal. In this way, it would be possible to draw up a correctly structured image report with a clinical impact and, at the same time, potential scientific significance. Reaching a good inter-observer reproducibility in interpreting the results through a well-accepted classification system such as IMPeTUs could improve the extrapolation of prognostic data from PET images and patients’ risk stratification guiding clinicians in the identification of the best personalized treatment for each patient. Examples of the usage of IMPeTUs criteria for PET findings are given in Figures 2 and 3.
Figure 2. A representative example of hot spots with no underlying lytic lesions. (A) positron emission tomography (PET) axial cut, (B) computed tomography (CT) axial cut, (C) fused images axial cut of two focal uptakes localized on the left acetabulum and coccygeal bone, respectively. Extranodal involvement is also evident on the left side. In this case, IMPeTUs criteria would have been scored as BM2 (normal bone marrow), F2 (two focal hot lesions) with DS4Sp (spinal) and ExP (extraspinal in the rib), EMsk (extramedullary skin).

Figure 3. A representative example of hot spots with lytic lesions underlying (A,G) PET axial cut; (B,H) CT axial cut; (C,I) fused images axial; (D) PET sagittal cut; (E) CT sagittal cut; (F) fused images sagittal cut showing active disease in the spine (A–D), sacrum (G–I) and in the seventh rib on the left. (A–C). A pelvic subcutaneous lesion is also evident (G–I). In this case, IMPeTUs criteria would have been scored as BM4 (increased bone marrow uptake), F2 (three focal hot lesions) with DS4Sp (spinal) and ExP (extraspinal in the rib), EMsk (extramedullary skin).

More recently, a joint analysis of a subgroup of newly diagnosed transplantation-eligible patients with MM enrolled in two independent European randomized phase III trials (IFM/DFCI2009 and EMN02/HO95) was performed by Zamagni et al. using the same approach [39]. The analysis of enrolled patients showed that focal or diffuse bone marrow FDG uptake lower than the liver background after therapy was an independent predictor for improved PFS and OS. The authors consequently proposed this criterion as
the gold standard for a PET complete metabolic response definition for patients with MM, further confirming the Deauville score’s value in patients with MM.

5. Diagnostic and Prognostic Value of FDG PET/CT in the Response Assessment in Multiple Myeloma

As detailed in Table 1, several studies assessed the diagnostic accuracy of FDG PET/CT in the response assessment. Derlin et al. retrospectively compared FDG imaging and whole-body MRI to determine the remission status after BM Transplant (BMT) [25], showing that the former approach was more specific (85.7% vs. 38.1%) for the identification of the remission status due to the lower incidence of false-positive findings. Superimposable results were prospectively observed by Basha et al. [34]. However, the addition of functional parameters (such as ADC) to MRI may favorably impact the specificity of this tool, improving its performance in the response assessment [40]. On the other hand, FDG PET/CT sensitivity may not be uniformly high as it can be lower to the pretreatment phase due to the functional bone marrow FDG uptake, which may reduce the signal to noise ratio [11]. Furthermore, it may depend on the disease category according to the Uniform Response Criteria for myeloma [11]. However, emerging data has shown that dual time point imaging might favorably impact this limitation. Indeed, in a small prospective study by Zirakchian Zadeh et al. [41] observed that the bone marrow FDG uptake between two acquisition time points (at 1- and 3-h post-injection) increased significantly in patients with a poor response to treatment but not in patients that achieved a complete response. This finding might potentially improve FDG PET/CT sensitivity in this differential diagnosis. However, larger studies are needed to confirm this initial evidence.

In addition to its diagnostic value, several studies have underlined that the prognostic significance of FDG PET/CT in the post-treatment setting could guide the subsequent clinical management in MM (Table 1). Bartel et al. [16] performed a subanalysis of the Total Therapy 3 Trial [60], showing that candidates to BMT who did not achieve a complete FDG suppression after induction chemotherapy were characterized by an inferior long-term prognosis. The same results were confirmed by other studies [16,23,27,33,36], supporting the use of serial FDG PET/CT to individualize patient therapy and (eventually) to rapidly move to alternative therapies in the presence of persistent PET positivity before BMT. Of note, the predictive value of the pre-BMT persistent FDG positivity largely overcame one persistent MRI abnormality [16]. The persistence of metabolically active disease (particularly in the extramedullary sites) predicts unfavorable outcomes in the post-BMT setting, being associated with higher relapse rates and shorter PFS and OS [26,28,32,33,37].

6. Unmet Needs and Open Issues

Despite the increasing FDG PET/CT role in MM, several issues remain unsolved, particularly in response assessment. First, the exact timing for the PET/CT treatment monitoring is currently lacking as a high heterogeneity in the time of imaging was observed in the analyzed studies. In most cases, post-therapy FDG PET/CT imaging was performed after at least three months from chemotherapy initiation [5,6,12,19,21,25,28,29,37,38]. A few studies [12,23,24] showed the potential utility of a very early response assessment (after one to three cycles of chemotherapy) in predicting the subsequent clinical outcome. In three studies, the post-treatment evaluation timing was pre-BMT setting (after induction chemotherapy) [16,27,39], while a few studies focused on the long-term post-BMT set [11,25].

In addition to its timing, the FDG PET/CT’s exact impact on the subsequent clinical management still needs to be defined. Indeed, there is no study supporting the usefulness of an early treatment change based on the FDG PET/CT result, mainly when it happens in the absence of new osteolytic lesions.

Third, the optimal definition of a metabolic response after treatment is still lacking, hampering meaningful comparisons between the analyzed studies. However, as detailed above, introducing highly reproducible Deauville-derived interpretation criteria represents a promising step toward harmonization in this field.
As a final remark, it should also be noted that both false-positive and negative results may occur when monitoring the response using FDG imaging in MM. Consequently, it is reasonable that in specific clinical situations, approaches other than FDG-PET/CT may be more appropriate to evaluate MM’s response to therapy.

7. Non-FDG PET Tracers in the Post-Treatment Setting of Multiple Myeloma

In the last years, several new tracers beyond FDG have also been tested in patients with MM (Table 2).

One of the first non-FDG tracers used in this setting is $^{11}$C-methionine (MET). MET is able to reflect the synthetic protein turnover by malignant cells and its uptake is not influenced by non-disease related determinants of bone marrow tracer uptakes such as anemia or systemic inflammation. This feature results in a good sensitivity concerning FDG in describing the degree of bone infiltration in the staging phase [61–63], even when low monoclonal protein-producing myelomas such as IgD, IgE and non-secretory types are studied [64]. The higher adherence of MET uptake (compared with FDG uptake) to the proliferative activity of MM resulted also in a higher sensitivity in the detection of minimal residual disease in a young patient with an unusual extramedullary (vulvar) presentation of recurrent MM [65]. On these bases, MET-PET/CT was also tested in the response assessment to therapy. Luckerath et al. [66] compared FDG- and MET-PET/CT in the monitoring of responses with anti-myeloma therapy and outcome prediction in MM’s mouse model. The authors showed that MET was more sensitive than FDG in the very early response assessment as CD138 expression reduction on the MM cellular surface was better correlated with MET uptake than FDG [67]. In turn, this variation in tumor biology correlated with survival [66]. Whether confirmed in humans, MET-PET imaging would establish a novel approach for treatment individualization, allowing for therapy initiation and adjustments earlier than any other existing method, even outperforming analysis of free light chains [66].

Other tracers such as NaF, choline, acetate, FLT and PSMA already included in the evaluation of cancer patients in different clinical settings have also been proposed in the field of MM [31,38,68–72]. Preliminary evidence in the preclinical setting and small groups of patients are also available with other tracers such as $^{68}$GaPentixafor [73], 18F-Fludarabine [74] and a radiolabeled anti-CD138 murine antibody [75]. However, these studies mostly focused on the PET detection of MM lesions rather than the response to therapy or residual disease detection.
Table 2. Non-2-deoxy-2-[18F]fluoro-D-glucose (FDG) PET tracers in the post-treatment setting of multiple myeloma.

| Ref  | First Author, Year | Country     | Number of Patients | Population          | Tracer | Study Design | Administered Therapy | Timepoint                  | Follow-Up Duration | Images Evaluation                | Endpoint/Gold Standard | Major Findings                                                                 |
|------|--------------------|-------------|--------------------|---------------------|--------|--------------|----------------------|--------------------------|----------------------|-------------------------------|----------------------|--------------------------------------------------------------------------------|
| [70] | Lin, C., 2014      | Taiwan      | 13/15              | MM                  | ACT    | PCS          | Induction therapy    | Baseline and post-induction therapy | 4 months             | Qualitative, semiquantitative (SUVmax) | CO, FDG PET/CT, MRI       | Acetate PET/CT showed a higher detection rate for myeloma lesions at diagnosis than using 18F-FDG and may be valuable for response evaluation |
| [65] | Caldarella, C., 2017| Italy       | 1                  | Extramedullary relapse of MM | MET    | RS           | CTx                  | Baseline and post-CTx | n.a.                   | Qualitative                   | FDG PET/CT             | Additional role of MET PET/CT in comparison with FDG PET/CT in depicting possible residual disease after treatment in extramedullary vulvar relapse of MM in a young patient |
| [64] | Imataki, O., 2017  | Japan       | 1                  | Serologically less active myeloma | MET    | RS           | CTx                  | Baseline and after CTx | n.a.                   | Qualitative                   | FDG PET/CT             | Met-PET/CT is more sensitive than FDG-PET in patients with serologically less active myeloma. Pentixafor PET/CT provides further evidence that CXCR4 expression frequently occurs in advanced MM, representing a negative prognostic factor and a potential target for specific treatment |
| [73] | Lapa, C., 2017     | Germany     | 35                 | MM                  | Pentixafor | RS          | CTx + 28/35 auto-BMT| After CTx + 28/35 auto-BMT | n.a.                   | Qualitative, semiquantitative (SUVmax, SUVmean) | OS, PFS, FDG PET/CT     | MET PET/CT shows higher sensitivity in comparison with standard FDG to detect intra and extramedullary MM                                                             |
| [62] | Lapa, C., 2017     | Germany and Spain | 78                | Plasmacytoma, SMM, MM | MET    | PCS          | Baseline or CTx/RT/auto-BMT | Baseline or after therapy | n.a.                   | Qualitative, semiquantitative (SUVmax) | Histologic plasma cell infiltration, FDG PET/CT | NaF PET/CT did not aid significantly in treatment response assessment of MM patients, at least in an early phase |
| [31] | Sachpekidis, C., 2017| Germany     | 34                 | MM                  | NaF    | PCS          | CTx + auto BMT       | Baseline and after therapy | 15–52 months | Qualitative, semiquantitative (SUVmax, SUVmean) | OS, PFS, FDG PET/CT     | FLT does not seem suitable as a single tracer in MM diagnostics |
| [72] | Sasikumar, A., 2017| India       | 1                  | Plasmacytoma        | PSMA   | RS           | Baseline             | baseline                  | n.a.                   | Qualitative                   | FDG PET/CT             | PSMA PET/CT allows the imaging of MM                                               |
| [69] | Sachpekidis, C., 2018| Germany    | 12                 | MM, SMM             | FLT    | PCS          | Baseline or CTx + auto-BMT | 11/12 baseline | n.a.                   | Quantitative, semiquantitative (SUVmax, SUVmean), quantitative | FDG PET/CT             |                                                                                     |
| [66] | Lapa, C., 2019     | Germany     | 19                 | MM, plasmacytoma    | MET and choline | RS           | Baseline             | Baseline                  | n.a.                   | Qualitative                   | BM biopsy             | MET PET/CT could be more sensitive than choline PET/CT for the detection of active MM lesions |
| Ref    | First Author, Year | Country  | Number of Patients | Population | Tracer | Study Design | Administered Therapy | Timepoint                  | Follow-Up Duration | Images Evaluation             | Endpoint/Gold Standard | Major Findings                                                                 |
|-------|--------------------|----------|--------------------|------------|--------|--------------|---------------------|--------------------------|----------------------|-------------------------------|----------------------------|--------------------------------------------------------------------------------|
| [29]  | Nakuz, T.S., 2019  | Austria  | 7                  | MM         | NaF    | RS           | Baseline and after therapy | Baseline and after therapy | 7–22 months  | Qualitative, semiquantitative (SUVmax, SUVmean) | CO, BM infiltration, FDG PET/CT | NaF PET/CT as a marker of bone mineralization was shown to be significantly decreased after first-line therapy |
| [63]  | Morales-Lozano, M.I., 2020 | Germany | 22                 | MM         | MET    | RS           | Baseline             | Baseline                | n.a.                             | Qualitative, semiquantitative (SUVmax, SUVmean, SUVpeak, MTV), quantitative | CO, R-ISS, M protein concentration, FDG PET/CT | MET PET/CT is a more sensitive marker for the assessment of myeloma tumor burden than 18F-FDG |
8. Conclusions
In conclusion, FDG PET/CT has an established clinical value in the initial phase of MM. However, in the last ten years, emerging data have shown that this tool could be of a high value for monitoring the therapy response making FDG PET/CT the recommended imaging approach in this field. This has raised the need for standardized imaging evaluation criteria to uniformly estimate the metabolic response to treatment in clinical trials and everyday clinical practice. Non-FDG PET tracers may explore MM’s other biological features, thus further improving the response assessment of plasma cell disorders.

Author Contributions: All authors have contributed to the literature search and have drafted and revised the text. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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