



ADVANCES IN MULTIPLE MYELOMA

Imaging in multiple myeloma: How? When?

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Bone disease is the most frequent feature of multiple myeloma (MM) and represents a marker of end-organ damage; it is used to establish the diagnosis and to dictate the immediate need for therapy. For this reason, imaging plays a significant role in the management of MM patients. Although conventional radiography has traditionally been the standard imaging modality, its low sensitivity in detecting osteolytic lesions and inability to evaluate response to therapy has called for the use of more sophisticated techniques, such as whole-body low-dose computed tomography (WBLDCT), whole-body magnetic resonance imaging, and ¹⁸F-fluorodeoxyglucose–positron emission tomography/computed tomography (PET/CT).

In this review, the advantages, indications of use, and applications of the 3 techniques in the management of patients with MM in different settings will be discussed. The European Myeloma Network and the European Society for Medical Oncology guidelines have recommended WBLDCT as the imaging modality of choice for the initial assessment of MM-related lytic bone lesions. Magnetic resonance imaging is the gold-standard imaging modality for detection of bone marrow involvement, whereas PET/CT provides valuable prognostic data and is the preferred technique for assessment of response to therapy. Standardization of most of the techniques is ongoing. (*Blood*. 2019;133(7):644-651)

The role of imaging in multiple myeloma and the “death” of conventional radiography

Bone disease is the most frequent feature of multiple myeloma (MM), occurring in approximately two thirds of patients at diagnosis and in nearly all patients during their disease.¹ Despite remarkable advances in MM therapy over the last decade, the consequences of skeletal involvement still remain clinically relevant. Bone disease impairs patients' quality of life and represents a major cause of morbidity and mortality. For this reason, imaging plays a very important role in the management of MM.² First, it is necessary for detection of lytic bone lesions, which represent a marker of disease-related end-organ damage and are traditionally used to diagnose MM and to establish the need for immediate therapy.³ Additionally, imaging could identify sites of extramedullary disease (EMD), which represent an unfavorable prognostic feature, and it helps to accurately differentiate between solitary plasmacytoma (SP) and MM, as well as to predict the risk of early progression from smoldering MM (SMM) to active disease. During the course of MM, imaging is also essential to establish the diagnosis of relapse and, eventually, to detect sites of bone damage at potential risk for pathological fractures or neurological complications. Lastly, functional imaging techniques enable more careful assessment of the depth of response to treatment, in particular in patients with nonsecretory MM and normal serum-free light chain (sFLC) ratio²; more generally, they contribute to the definition of negative minimal residual disease (MRD).

Although conventional radiography has historically been the standard imaging technique for many years, it has several

limitations. For a lytic lesion to become apparent, it involves losing >30% of trabecular bone. Other limitations include the prolonged study time, difficulty in assessing certain areas (eg, pelvis and spine), inability in distinguishing vertebral fractures secondary to benign osteoporosis from those related to the underlying MM clone, and limitation in the assessment of response to treatment as a result of the low sensitivity of the technique for the limited bone healing. Recently, 2 retrospective trials on a large number of patients with suspected SMM, who received skeletal survey and either positron emission tomography/computed tomography (PET/CT)⁴ or whole-body low-dose computed tomography (WBLDCT)⁵ as part of their diagnostic work-up, demonstrated that the use of conventional radiography would have underestimated the presence of bone disease in ~25% to 40% of cases. Limitations of conventional radiography led to increasing use of more advanced imaging modalities. In 2014, the International Myeloma Working Group (IMWG) updated the diagnosis of MM and established that >1 lytic lesion seen on computed tomography (CT), WBLDCT, or PET/CT, regardless of its detection or not on skeletal radiography, and >1 unequivocal (≥5 mm in size) bone marrow (BM) focal lesion (FL) on MRI fulfill the criteria for MM-related bone disease.⁶ These guidelines were introduced after the clear demonstration that the novel imaging techniques have a higher detection rate than skeletal survey⁷ and led to their routine use in clinical practice.

In this review, we discuss the advantages, indications of use, and applications of the main novel imaging techniques in MM and SMM patient management, as related to the diagnostic work-up

at diagnosis and subsequent relapse(s) and evaluation of response to therapy.

Novel imaging techniques for the diagnostic work-up of MM and SMM

Over the past years, the development of novel and more sensitive imaging methods for the identification of osteolyses has progressively led to their substitution for skeletal survey.

WBLDCT

WBLDCT was introduced to detect osteolytic lesions in the whole skeleton, with high accuracy, no need for contrast agents, and twofold to threefold lower radiation dose exposure compared with standard CT.^{8,9} In several studies, WBLDCT was found to be superior to whole-body X-ray in detecting osteolytic lesions, affording higher sensitivity and a higher detection rate, in particular in the spine and pelvis, resulting in higher accuracy.^{4,5,8-13} In addition, CT provides important information regarding the potential instability and fracture risk of the vertebrae, as well as being a guide for radiotherapy and surgery. The development of recommendations for WBCT protocols is ongoing; however, it is generally suggested that one perform a whole-body low-dose multidetector computed tomograph with 3.2 to 4.8 mSv as the radiation doses (skeletal survey referral: usually 1.2-4.8).¹⁴ Although the main role of WBLDCT is identification of bone destruction, BM plasma cell (PC) infiltration can be detected in the long bones in adults, which are generally substituted by fatty marrow. The detection of nodular or diffuse infiltration of long bones has proved to be of prognostic significance.¹⁵

¹⁸F-fluorodeoxyglucose-PET/CT

PET/CT, usually with ¹⁸F-fluorodeoxyglucose (FDG) as the radiopharmaceutical, is a dual technique that blends the ability to identify bone destruction and lytic lesions with assessment of tumor burden and disease activity, in different areas of the BM and of the cancellous and cortical bone.² This is of particular interest because BM PC infiltration in MM is not homogeneous.

PET/CT can be used for the diagnostic work-up of the disease, because several studies have reported a sensitivity and specificity for detection of bone lesions in the range of 80% to 100%.¹⁶⁻²⁰ The combination of functional imaging with positron emission tomography (PET) plus morphological assessment with CT makes this technique the most effective in identifying potential sites of EMD.²¹ In addition to the presence of EMD, the number and metabolism of FLs prior to treatment have been identified as predictors for clinical outcomes in several prospective or retrospective studies in patients eligible for autologous stem cell transplantation (ASCT) or allogeneic stem cell transplantation.^{17,18,22} The presence of >3 FDG-avid FLs is known to be an independent variable associated with inferior overall survival (OS) and progression-free survival (PFS). Additional prognostic information provided by PET/CT includes the level of FDG uptake, quantified as the maximum standardized uptake value.

Finally, as discussed in more detail in "Novel imaging techniques for assessment of response to therapy and during follow-up," performing PET/CT at baseline allows the assessment of the metabolic response to therapy by comparing pre- and posttreatment images.

The IMWG has published a consensus statement on the use and interpretation of FDG-PET/CT; FLs have been defined as having an FDG uptake higher than the hematopoietic BM and/or the liver, with a minimum diameter of 5 mm. Diffuse uptake is defined as uptake greater than that of the liver. The CT part of a PET/CT may be considered broadly comparable to a WBLDCT, according to the minimum technical requirements established by the IMWG.²³

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been established as a valuable technique for diagnosing bone involvement in MM.²⁴ MRI is based on examining the composition of the tissue with regard to water and fat content and has the highest sensitivity when it comes to detecting BM infiltration by myeloma cells, without radiation exposure. Conventionally, MM lesions on MRI are characterized by hypointensity in T1-weighted images and hyperintensity in T2-weighted images, with fat suppression in opposed-phase imaging and increased contrast enhancement in T1-weighted sequences. The intervertebral disk is usually identified as a reference for signal intensity. Depending on the MRI slice thickness, a minimum diameter of 5 mm is needed to define an FL. Five MRI patterns of marrow involvement have been recognized in MM: normal, focal, diffuse, combined focal and diffuse, and variegated or "salt and pepper."^{24,25} The field of view can be axial (spine and pelvis) or whole body. Contrast agents are usually based on gadolinium, which is relatively inert, although in the case of renal insufficiency, it can lead to a severe complication: nephrogenic systemic fibrosis. A contrast agent is not always needed, because nonenhanced MRI has a high resolution for the BM. Diffusion-weighted imaging (DWI) is an additional MRI protocol that measures the movement of water molecules in the tissue,²⁶ underlining the presence of high cellularity (limited movements), as opposed to low cellularity and/or higher microcirculation (increased movements), without the need for a contrast agent; the higher or lower cellularity is delivered with semi-quantitative parameters, such as the apparent diffusion coefficient (ADC). The correlation between ADC and histological infiltration by BM PCs has been clearly demonstrated.^{27,28}

Several studies have shown that MRI, either axial or whole body, is more sensitive than whole-body X-ray for the detection of bone involvement in MM, affording higher diagnostic precision.^{29,30} Studies that have compared MRI with PET/CT have shown that the 2 techniques are equally effective in detecting FLs.¹⁹ Studies comparing MRI with WBLDCT have suggested excellent agreement in terms of lesion detection, pattern, and BM involvement.³¹ MRI FLs correlate with standard known prognostic factors, in particular cytogenetics, and with clinical outcomes.^{29,32,33} On the contrary, the prognostic meaning of a diffuse pattern is less clear; addition of the DWI technique as an adjunct may clarify this issue.³⁴

The IMWG has published a consensus statement on using MRI²⁴; however, in light of the more recent development of whole-body MRI (WBMRI), and especially DWI MRI protocols, as well as the importance of uniform criteria for comparison of different studies and for clinical practice, more specific and technical new recommendations are currently under discussion.

Which imaging to choose?

There is considerable heterogeneity in clinical practice with regard to the incorporation of the different imaging modalities in patient management. The clinical use of different techniques is

Table 1. Comparison of novel imaging techniques as part of the diagnostic work-up regarding most relevant topics

	WBLDCT	PET/CT	MRI
Ease of use	Patient friendly (fast scanning time, <15 min)	Scanning time (including radiopharmaceutical injection) ~60 min	Variable scanning time (30-60 min)
	Relatively inexpensive	More expensive	More expensive
	Widely available	Not always available	Relatively available
Radiation exposure	Relatively low radiation dose (3-4 mSv)	Higher (6-10 mSv)	No radiation exposure
	No need for IV contrast administration		
Bone damage	Depicts lytic bone lesions	Depicts contemporary lytic bone lesions and/or EMD and disease metabolism	Highest sensitivity for early bone damage
Prognostic relevance	Not clear	Prognostic significance of FL number and SUV _{max} value	Prognostic significance of FLs and diffuse pattern
Favorite target	Gold standard for CT-guided biopsy, surgery, RT planning, evaluation of stability of fractures	Favored technique to assess EMD	Gold standard for detection of diffuse BM involvement, differential diagnosis between osteoporotic and pathological fractures, cord compression

RT, radiotherapy; SUV_{max}, maximum standardized uptake value.

often influenced by their availability, local expertise, affordability, and national guidelines for reimbursement. Likewise, international societies, such as the IMWG, the European Myeloma Network,³⁵ and the European Society for Medical Oncology,³⁶ have provided different recommendations. When making a choice, one should also remember that findings at baseline impact on interpretation of the same findings after therapy. Because the detection of lytic bone lesions, which are eventually at risk for developing possible complications, is the mainstay for starting anti-MM treatment and managing MM patients correctly, WBLDCT is considered in most guidelines and is routinely used in clinical practice as the standard technique for assessment of myeloma bone disease. Skeletal survey should only be applied if nothing else is available. If no signs of bone destruction are detected on CT, MRI, preferably whole body or at least of the axial skeleton, should be performed to establish the presence of >1 FL, which is now a myeloma-defining event according to the new diagnostic criteria.⁶ We recommend PET/CT if there is a strong suspicion of EMD, in cases of oligo-nonsecretory MM with normal sFLC ratio, or in clinical trials in which systematic MRD assessment is being applied, to create a baseline for response assessment. We believe that WBLDCT is a good compromise for all of the other patients. Table 1 summarizes the advantages of the 3 main imaging techniques for diagnostic work-up.

SMM

Highly sensitive imaging techniques are crucial in SMM, because tumor mass and BM infiltration are usually lower in this early phase of the disease. As already discussed, according to the new IMWG diagnostic criteria, a WBLDCT should first be applied to all suspected SMM, because identification of (even asymptomatic) lytic lesions shifts the diagnosis to MM.⁶ Again, skeletal survey should only be performed if more sensitive techniques are not available. Based on the IMWG consensus statement,⁶ if WBLDCT does not show any signs of bone destruction, an MRI, possibly whole body or at least axial, should be performed to look for FLs. Patients with >1 unequivocal FL on MRI should be

considered to have MM, requiring therapy.⁶ This was established on the basis of 2 studies showing that SMM patients with >1 FL on MRI (reported in 16% and 28% of cases) had a median time to progression to symptomatic disease of 13 to 15 months and a 2-year probability of progression of ~70% to 80%.^{37,38} In both studies, the presence of >1 FL on MRI was an independent adverse prognostic factor for progression to active disease. Patients with a single FL or >1 small (<5 mm) or equivocal FL should be considered for additional CT or PET/CT, if available, and should undergo a repeat MRI within 3 to 6 months. In these patients, an increase in the size or number of FLs dictates the start of therapy. In fact, it was shown that progression of FLs on MRI during the follow-up of SMM patients was a stronger predictor of transformation into active disease than baseline findings.³⁹ If no signs of progression occur in the first years, imaging frequency might be reduced, because the risk of progression of SMM into MM decreases over time.⁴⁰

Imaging might also be used to identify high-risk SMM patients^{41,42} who are candidates for clinical trials. From the imaging standpoint, in addition to the presence of a single FL or equivocal images, high risk can be defined when patients present a diffuse abnormality on MRI²⁴ or focal FDG uptake on PET/CT, without underlying osteolytic bone destruction.⁴³

In conclusion, we believe that WBLDCT to exclude active disease, and, if negative, axial/WBMRI to exclude the presence of >1 FL, should be applied to all SMM patients.

Novel imaging techniques for assessment of response to therapy and during follow-up

Importance of response evaluation outside the BM

Specific biomarkers of the tumor clone size, including the M protein, sFLC and heavy chains, and BM plasmacytosis,

represent the basic response criteria in MM and are commonly used for monitoring the course of the disease.⁶ However, BM PC infiltration is often patchy, thus increasing the likelihood of a false-negative assessment; in addition, BM evaluation does not allow one to identify EMD escape as a sign of metastatic spreading of the disease.⁴⁴ This phenomenon is increasingly being found, as a result of prolonged OS and widespread use of functional imaging techniques, and is associated with a dismal clinical outcome, even in the novel agent era.^{21,44-46} Moreover, it has recently been demonstrated by a prospective study, which serially monitored patients with functional imaging and FL biopsies, that MM entails spatial heterogeneity, with the possible coexistence of different disease clones, displaying different genomic profiles, in the BM and in FLs.⁴⁷ The larger the FL size, the greater the heterogeneity.⁴⁷

Nonetheless, development of sensitive techniques (cell based, molecular based, and imaging based) for response assessment and availability of highly effective novel agents, resulting in unprecedented rates of high-quality responses, have led to changes in the definition of response, and concepts, such as depth of response and MRD, have been introduced.⁴⁸ Extensive data indicate a clear association between depth of response and long-term outcomes; thus, MRD information can potentially be a reliable and early biomarker of treatment effectiveness.⁴⁹

To ensure complete eradication of the tumor, it is necessary to assess the extramedullary compartment in addition to BM. Extramedullary sites of clonal proliferating PCs, in a context of BM MRD negativity, are more frequent in patients with EMD at diagnosis (5% to 10%) or with paramedullary plasmocytomas.⁵⁰

Skeletal survey is useless when evaluating response to therapy, because of the low sensitivity of the technique for the limited bone healing,⁵¹ as well as for soft tissues/masses. Here, functional, rather than morphological, imaging techniques are the favored tools.²

¹⁸F-FDG-PET/CT

¹⁸F-FDG-PET is an excellent imaging tool to assess tumor metabolic activity and monitor response to treatment, because of its ability to distinguish between active and inactive (eg, fibrotic) disease. In addition, low-dose CT, which is typically done for localization, along with FDG-PET, constitutes a precise screen for bone and extramedullary findings.²

Several studies have demonstrated a prognostic role for PET-positive lesions after completion of therapy.^{17,18,45} It has also been reported that PET/CT negativity correlates well with the achievement of high-quality response to therapy.^{17,18} In 2 studies, FDG-PET/CT was evaluated very early (eg, on day 7) after induction treatment⁴⁵ or before the first ASCT.¹⁸ Persistence of >3 FLs at day 7 predicted significantly shorter PFS and OS, especially in the subgroup of patients with gene expression profiling-defined high-risk MM.⁴⁵ By contrast, complete FDG suppression in FLs before ASCT was associated with significantly longer PFS and OS. Negative PET/CT scans preceded the achievement of conventionally defined complete response (CR), whereas a normal MRI pattern was reached later.¹⁸ In an additional study, permanence of high-tumor metabolism after thalidomide-dexamethasone induction treatment was an early predictor of worse PFS after ASCT, whereas after double ASCT,

PET/CT negativity was an independent factor related to durable disease control and prolonged OS.¹⁷ In a third prospective series of 134 newly diagnosed ASCT-eligible MM patients who were scheduled to receive a triplet regimen comprising bortezomib, lenalidomide, and dexamethasone, followed or not by upfront ASCT and 1-year maintenance therapy with lenalidomide, FDG-PET/CT was evaluated after induction therapy and prior to maintenance.¹⁹ Normalization of PET/CT scans after induction therapy (32% of the patients) was associated with a significant improvement in PFS, whereas PET/CT negativity before starting maintenance therapy (62%) predicted improved PFS and OS. Moreover, the prognostic value of PET/CT was independent of and complementary to MRD evaluation within the BM by flow cytometry at a sensitivity level of 10⁴.¹⁹ Additional studies, including smaller numbers of patients, confirmed the value of FDG-PET/CT, combined with laboratory parameters, in predicting the risk of progression after high-dose or conventional-dose therapies, regardless of whether any of the novel agents were included.^{22,52,53} In addition, it has recently been demonstrated that the prognosis of patients who obtain PET FL normalization during or after the end of therapy is comparable to that of patients without increased metabolism at baseline, suggesting the value of treating until suppression of glucose metabolism.⁵⁴ Finally, an overview of the literature consisting of 6 prospective and 4 retrospective studies including 690 patients with MM or SP provided evidence that FDG-PET/CT helps to assess the extent of response to treatment and early detection of recurrence sites.⁵⁵

With regard to MRD evaluation in patients achieving CR, FDG-PET/CT negativity after ASCT predicted a lower risk for progression or death in patients with conventionally defined CR than in patients with metabolically active sites of disease.¹⁷ In a retrospective study of 189 transplant-eligible and -ineligible patients, FDG-PET/CT was evaluated at diagnosis and after the end of treatment. Conventionally defined CR was achieved in 53% of cases, but, in 29%, PET/CT remained positive. For these latter patients, the median PFS and OS were significantly shorter than for those with normalizing PET/CT scans. On multivariate analysis, posttreatment PET/CT negativity proved to be an independent factor predicting prolonged PFS and OS.⁵⁶ In an additional study, the finding of PET negativity within patients achieving high-quality response after ASCT correlated with significantly improved PFS and OS.⁵² By contrast, in a prospective study of 45 newly diagnosed MM patients treated up front with a highly effective triple combination of second-generation novel agents, no relationship was found between the degree of PET/CT response and clinical response, MRD status, or PFS.⁵⁷

On the basis of the above-reported results, ¹⁸F-FDG-PET/CT is considered the preferred imaging technique for evaluating and monitoring metabolic response to therapy.²³ Note, however, that false-negative and -positive results may occur with the use of FDG-PET/CT. In particular, false-negative scans may relate to hyperglycemia or recent administration of high-dose steroids, leading to transient metabolic suppression. Moreover, it has been reported that, in a variable proportion of patients (10%-15%), PCs may not be ¹⁸F-FDG avid, as a result of the lack of hexokinase enzyme, which is responsible for FDG trapping in the cells.⁵⁸ In these patients, FDG-PET/CT is not an appropriate tool to evaluate metabolic response to therapy. In addition to

Table 2. Comparison of novel functional imaging techniques for assessment and monitoring of response to therapy

	PET/CT	Functional MRI
Studies available to date	Results reproduced in large prospective independent studies	Results reproduced in independent series of patients, even if mainly retrospective and heterogeneous populations
Prognostic relevance	Predicts high risk of early progression for patients with residual FLs	Possesses the higher reliability for diffuse BM infiltration
	Refines the prognosis of patients in conventionally defined CR	Demonstrated early changes during treatment
	Defines the imaging MRD-negative response category	
	Is complementary to BM cellular or molecular-based techniques	
	Contributes to define the sustained MRD-negative response category, associated with the best patient outcomes	

¹⁸F-FDG, new PET/CT tracers that target different metabolic pathways or receptors expressed by PCs and act as potentially more sensitive and specific molecular imaging biomarkers have been investigated preliminarily in a limited series of MM patients or in mouse models.⁵⁹⁻⁶³ Radiolabeled antibody imaging may be advantageous, as is imaging tumor cells with antigenic expression, regardless of metabolic processes, resulting in earlier and more specific assessment of response. However, the lower availability of these newer tracers, interpatient tumor heterogeneity with regard to specific targets, and the lack of prognostic data and standard reporting prevent any definite conclusion from being drawn. On the other hand, standardization of FDG-PET/CT is ongoing, through an accurate descriptive analysis based on Deauville criteria applied to lymphomas, followed by a combined analysis of prospective trials.⁶⁴

MRI

MRI is the elective imaging technique to assess the degree of BM PC infiltration, even before bone destruction is present, owing to its ability to visualize large volumes of BM.²⁴ Thanks to its high sensitivity and spatial resolution, it is particularly useful for settings in which the tumor burden is low (eg, early stages or after systemic therapy). Changes in MRI patterns may correlate with response to therapy and may be used to assess the effects of antimyeloma treatment. In particular, MRI functional approaches, like dynamic contrast-enhanced imaging and DWI, are the favored tools to evaluate the disease after therapy. Although some studies showed an improved OS for patients displaying FL resolution by standard MRI,^{29,65} this technique is associated with a high incidence of false-positive results, because lesions do not resolve, but undergo necrotic changes, and remain visible even when without any vital cells. The recent development of whole-body DWI MRI enables quantitative assessment of disease burden, measuring the ADC, influenced by tissue microarchitecture and related to marrow cellularity.^{66,67} Whole-body DWI MRI is also a powerful imaging tool for the detection of diffuse marrow disease. Initial experience with whole-body DWI MRI in small numbers of MM patients in different phases of disease showed the technique to be highly sensitive, especially in detecting diffuse marrow disease, giving a higher correlation with BM trephine samples than PET/CT⁶⁸ and displaying significant changes in ADC in patients in remission after therapy, early on and at the end of treatment.^{27,66,69-74}

At this time, widespread use of DWI MRI to assess metabolic response to therapy is hampered by the lack of consensus on acquisition, interpretation, and reporting of the results, which

Table 3. Validated points and issues to be addressed by ongoing trials

Validated points
Novel imaging techniques are more sensitive than skeletal survey and are correctly distinguishing SMM from MM from SP
WBLDCT is the minimal requirement for detection of lytic lesions
MRI is the best imaging modality for assessment of BM involvement
PET/CT is the preferred technique for detection of EMD
FLs display prognostic significance for PFS and OS
Functional imaging techniques are required for evaluation of metabolic response to therapy
PET/CT is the preferred technique to evaluate MRD after therapy
MRD by NGS or NGF and PET/CT are complementary
Open issues
Standardization and guidelines for acquisition, interpretation, and reporting of all 3 imaging techniques
Correlation of new PET tracers with outcomes
Correlation of DWI MRI with outcomes
Prospective comparison of PET/CT and functional MRI after therapy
Optimal timing of PET/CT and DWI MRI for evaluation of response and during follow-up
Concordance between imaging and NGS/NGF MRD negativity, at different sensitivity thresholds
Contribution of imaging to the definition and loss of sustained MRD negativity
Impact of MRD assessment on treatment strategies

NGF, next-generation flow cytometry; NGS, next-generation sequencing.

must take into account differences in the microenvironment and cellularity that are due to age and to ongoing treatment causing necrosis.⁷⁵ Attempts in this direction are being made by an interdisciplinary group of radiologists and clinicians.

Which imaging to choose?

In light of the above-reported prospective trials, FDG-PET/CT is the best imaging technique for evaluating and monitoring response to therapy and correlating posttreatment findings with outcomes. We recommend performing PET/CT in each patient evaluated for MRD after therapy. The strength of PET relies on its ability to differentiate cellular tissue from necrosis, which is crucial when evaluating residual findings after therapy. However, the potential limitations of PET with FDG have also been discussed. Moreover, we lack homogeneous and prospective data on how whole-body DWI MRI performs in evaluating response to therapy in comparison with FDG PET/CT. If imaging evaluation is negative after therapy, there is no demonstrated role for serial evaluation until relapse. In patients with residual lesions, yearly follow-up is recommended, because these patients have a high risk for early progression.⁵⁶ Table 2 summarizes the advantages of functional imaging techniques in this setting.

Novel imaging techniques for the work-up of MM at relapse

In patients with MM and suspected relapse, the diagnosis requires direct indicators of tumor growth (≥ 1 of the clone-related biomarkers) and/or the presence of organ damage, including bone. For this purpose, WBLDCT should be the first choice, because it is recommended at diagnosis. If a biochemical progression is present or a disease with low tumor burden, MRI or PET may be preferable, for consistency with previous recommendations in SMM. In patients who display a nonsecretory or oligo-secretory phenotype at the time of disease progression, PET/CT is preferable to provide an objective marker of disease activity in that situation.⁷⁶ PET/CT was demonstrated to be a predictor of clinical outcomes in this setting, as well.^{77,78}

Open issues and future steps

Despite significant advances in the development and availability of novel imaging techniques for the management of MM, several issues need to be investigated further, especially with regard to MRD evaluation outside the BM, using functional techniques.⁷⁹ To propose the widespread use of imaging for the evaluation of metabolic response to therapy, outside clinical trials, several

points need to be addressed (Table 3). First, standardization of guidelines for acquisition, interpretation, and reporting of the techniques should be achieved. Attempts in this direction are currently proceeding for FDG PET/CT, WB MRI, and WBLDCT. To implement the sensitivity and diagnostic accuracy of functional techniques, newer PET/CT tracers have been preliminarily investigated, and DWI MRI has been tested, at different time points. Both of these techniques need to be explored further and correlated with clinical outcomes. In addition, a prospective comparison between DWI MRI images and PET/CT scans, before and after treatment, is needed to define whether an optimal technique can be identified for different patient subgroups and disease settings, during or after treatment. Moreover, it is important to establish the concordance between complete metabolic response and flow or sequencing MRD negativity at the BM level, with different sensitivity thresholds (10^{-5} - 10^{-6}) and to confirm the complementary role of imaging with cellular or molecular-based tools for the detection of MRD inside and outside the BM. Likewise, the contribution offered by imaging techniques, and optimal time points for their assessment, to the definition of sustained MRD negativity, as well as of its loss, should be determined. Finally, the impact of MRD assessment on treatment strategies still needs to be defined. Upcoming prospective trials that extensively apply novel techniques to evaluate MRD inside and outside the BM will help to address these issues and define the role of these promising tools in clinical practice.

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Footnote

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