The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma

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ABSTRACT

Multiple myeloma is the second most common hematologic malignancy and occurs most commonly in elderly patients. Almost all multiple myeloma patients develop bone lesions in the course of their disease or have evidence of bone loss at initial diagnosis. Whole-body conventional radiography remains the gold standard in the diagnostic evaluation, but computed tomography, magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography are increasingly used as complementary techniques in the detection of bone lesions. Moreover, the number of lesions detected and the presence of extramedullary disease give strong prognostic information. These new techniques may help to assess treatment response in solitary plasmacytoma or in multiple myeloma. In this article, we review recent data on the different imaging techniques used at diagnosis and in the assessment of treatment response, and discuss some current issues.

Introduction

The diagnosis of multiple myeloma (MM) requires three criteria: a monoclonal protein detectable in the blood and/or urine, 10% or over monoclonal plasma cells in the bone marrow (BM) and/or biopsy-proven plasmacytoma, and myeloma-related organ damage.[1] The features of this organ damage are denoted by the acronym CRAB and defined as the presence of Calcium elevation, Renal insufficiency, Anemia, and/or Bone disease manifested by osteolytic lesions or osteoporosis.[1] Initially, the Durie and Salmon Staging system recommended the whole-body X-ray skeletal survey (WBXR) as the gold standard to evaluate the extent of bone involvement. Since the 1980s, considerable technological advances in medical imaging have propelled computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) to the forefront. The integration of these imaging techniques in the diagnosis and staging of patients could potentially change disease management, because of their ability to detect active MM lesions with negative X-rays, in patients with a hyposecretory disease or in patients with extramedullary disease (EMD).

Methods

A comprehensive literature search of the PubMed and Scopus databases and abstracts presented at the ASH meetings was carried out to find relevant peer-reviewed articles on the use of MRI, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), PET/CT and CT in the diagnosis and monitoring of treatment response in patients with MM. Unless stated otherwise, the retained sensitivity and specificity values are related to the results obtained with WBXR. The detection rate of the different techniques was calculated by dividing the total number of lesions detected by MRI or PET/CT by the total number of lesions detected by WBXR or CT. Forest plots were created to illustrate the odds ratios for a shorter progression-free or overall survival of different laboratory or imaging variables. They were generated using Graphpad Prism, by introducing the odds ratios and standard errors reported from the original publications.

Advantages and limitations of the imaging techniques in MM

Plain X-rays or skeletal survey

Osteolytic lesions related to MM are most commonly found in the axial skeleton, skull, shoulder girdle, proximal humeri, ribs, and proximal femurs.[2] These lesions are generally investigated by WBXR, which consists of a series of plain X-rays that include the chest, skull, humeri, femurs, and pelvis, as well as antero-posterior and lateral images of the whole spine. According to the current guidelines of the International Myeloma Working Group, WBXR is considered as the gold standard imaging modality.[3] However, this technique has significant limitations. First of all, WBXR is insensitive to detect early osteolytic bone lesions and can, therefore, underestimate the extent of BM involvement.[4] An experimental study showed that a bone defect in a lumbar vertebra can be seen on lateral X-ray only when 50-75% of the trabecular bone has been destroyed.[5] Additionally, because WBXR requires 20 separate films, the patient generally spends a long period of time on the radiographic table. Furthermore, the WBXR cannot be used to assess treatment response, as the appearance of osteolytic lesions may not change following therapy.

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Computed tomography

CT allows the detection of small osteolytic lesions that are not revealed by plain radiography. In addition to the detection of bone destruction and soft tissue masses, CT provides a more comprehensive assessment of the fracture risk and the stability of collapsed vertebrae. CT is generally helpful in the planning of radiotherapy or a surgical intervention.[6,7] The sensitivity of whole-body multidetector CT to detect osteolysis is superior to that of WBXR, particularly for lesions located in the spine, pelvis or thoracic cage.[6,8,9] Furthermore, extramedullary lesions may be seen at CT. CT can also identify spinal cord and/or nerve root compression when MRI is not available. Current protocols try to reduce radiation exposure while preserving image quality by applying "low dose" protocol.[6,8]

Magnetic resonance imaging

Both WBXR and CT detect bone destruction related to the presence of MM cells in the BM. BM infiltration by MM cells can be directly visualized with MRI without radiation exposure and in an acceptable amount of time.

Four patterns of marrow involvement have been identified: a normal marrow appearance, a focal pattern, a diffuse pattern, and a variegated or micro-nodular (also termed salt-and-pepper) appearance.[10] Furthermore, a combination of these patterns may be present. A focal as well as a diffuse infiltration pattern carries an adverse prognostic value in both symptomatic and asymptomatic MM.[11-13] Bone lesions often include cortical breakthrough and extension into the soft tissues. A finding of epidural extension arouses particular concern because of the potential for cord compression, an oncological emergency.

The principal studies on the diagnostic capacities of MRI are recapitulated in Table 1. MRI focused initially on the axial skeleton (the entire spine, pelvis and proximal femurs). Lecouvet *et al.* compared axial MRI with the WBXR and found that MRI had a higher detection rate but that the WBXR was superior overall because it demonstrated more appendicular lesions.[14] When a whole-body examination is performed that includes at least the proximal appendicular skeleton, MRI has a higher detection rate than WBXR.[17] A direct comparison of axial MRI *versus* WB-MRI revealed that approximately 10% of patients show lesions exclusively outside the axial skeleton.[21] Baur-Melnyk *et al.* compared whole-body MRI with whole-body CT and found that MRI revealed more extensive disease in half of the patients.[18]

A systematic review of the role of imaging techniques in the diagnosis of myeloma bone disease compared MRI with WBXR and/or CT.[22] In the included studies, this detection rate of MRI ranged from 1.12 to 1.80 compared to WBXR, with a mean sensitivity of 95.3% compared to WBXR. MRI detected more lesions in the axial skeleton compared to WBXR, but WBXR detected more lesions in the ribs than MRI.

To improve the detection rate of MRI, several functional techniques (dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging) have been investigated.[23,24] These techniques allow at least semi-quantitative measurements of the microcirculation and cellularity, and first results have demonstrated their potential value for diagnosis and treatment monitoring in MM.[23,25,26] Hillengass *et al.* evaluated DCE-MRI of the lumbar spine in 222 patients with MGUS, SMM, and MM and 22 healthy controls.[27] They found significant differences between MM patients and normal controls, and were able to correlate the DCE-MRI peak intensity with the BM plasmacytosis.

Positron emission tomography-computed tomography

Positron emission tomography-computed tomography combines the imaging of a particular molecular process (depending on the injected radiopharmaceutical) with the morphological images provided by CT data. The FDG, a glucose analog, is the most widely used radiopharmaceutical agent in the diagnosis, prognosis estimation and treatment response assessment in different cancers, including high-grade lymphomas.[28]

In contrast to WBXR, that shows osteolysis related to the presence of MM cells, FDG-PET allows direct visualization of the tumor burden. It is important to emphasize that false negative or false positive findings (in case of other infectious or inflammatory processes) may be seen. Another limitation of PET/CT imaging is its low spatial resolution (6-8 mm), which may limit the detection of subcentimetric lesions. The combined CT component allows a direct anatomic correlation of FDG uptake foci and provides high-resolution bone images that allow a higher delection rate of lytic bone lesions than that achieved with plain radiography.[4,9,29]

The systematic review reported by Regelink *et al.* also compared FDG PET and FDG PET/CT with WBXR and CT.[22] Compared with WBXR, the detection rate of FDG PET/CT ranged from 1.27 to 1.45; sensitivity varied from 67 to 100% and specificity was low (29-50%) when using WBXR as the reference test. Regelink *et al.* mentioned that FDG-PET missed rib lesions but currently hybrid PET/CT systems are installed worldwide, and the low-dose CT of the PET could be able to detect additional rib lesions. However, skull lesions may be missed with FDG-PET/CT mainly due to the high FDG uptake in the brain. Finally, an optimized identification of extramedullary disease was uniformly reported in the studies comparing FDG-PET/CT with WBXR.

Beyond FDG reflecting glucose metabolism, other PET radiopharmaceuticals have been developed to image various biological processes. 18F-fluoride is currently being re-evaluated for skeletal imaging,[30] while the amino acid analog 11C-methionine and 11C-choline, a precursor analog of phosphatidylcholine, a major constituent of membrane lipids, have been evaluated in small series of MM patients.[31,32]

The different entities of malignant gammopathies

Smoldering myeloma

Smoldering or asymptomatic MM (sMM) accounts for approximately 15% of all cases with newly diagnosed MM and is characterized by a risk of progression to symptomatic myeloma. In this setting, diagnostic imaging examinations are crucial for the identification of lytic bone lesions and can also give prognostic information on the risk of progression. Molopoulos *et al.* analyzed spinal MRIs in 38 sMM patients and found a normal pattern in 19 patients, while the remaining patients had variegated, diffuse or focal patterns.[33] The median time to progression to symptomatic MM for all patients was 29 months; however, progression was delayed in patients with normal MRIs *versus* abnormal MRIs (43 *vs.* 16 months).[33] This group investigated the prognostic value of several laboratory and

radiological examinations and identified myeloma cell infiltration, the M-protein levels, free light chain (FLC) ratios and the MRI pattern as risk factors for progression.[34] In their study, the hazard ratio (HR) for patients with an abnormal MRI was calculated at 5.8 (1.84-18.35), and 5 of 8 patients with abnormal MRI progressed within 18 months. In multivariate analysis, a highly abnormal (> 100) FLC ratio and a BM infiltration of over 60% were the only independent risk factors for progression with an HR of 9 (95%CI: 2.15-39) and 13 (95%CI: 4.42-42.2), respectively (illustrated in Figure 1A).[34]

The Heidelberg group investigated the prognostic significance of WB-MRI in SMM and retained the presence of focal lesions on WB-MRI as the strongest adverse prognostic factor for progression to symptomatic MM. Multivariate analysis of the MRI and non-MRI parameters revealed that the presence and the number of focal lesions (HR: 3.01), as well as a diffuse bone marrow infiltration in MRI (HR: 2.37), remained the only significant prognostic factors for progression (illustrated in Figure 1A).[12] The same group recently reported their data on WM-MRI in 544 untreated patients with MGUS (n=138), sMM (n=157) and MM (n=249). The authors identified focal lesions in 34% and 80% of patients with sMM and MM, respectively, and a diffuse infiltration in 46% and 72% of the patients in both groups.[35] In approximately 66% of the patients with smoldering MM, the patterns of BM infiltration on MRI were similar to MGUS patients; whereas 34% showed patterns similar to MM

Table 1. Diagnostic studies on magnetic resonance imaging.

	Author (ref)	Patients	N.	Examinations	Reference	Key findings
AXIAL MRI	Walker, 2007[11]	Symptomatic MM (newly diagnosed)	611	Axial-MRI	WBXR	- 51% of patients showed focal lesions on both exams. - MRI detected a focal lesion in 52% of patients with negative WBXR, while WBXR detected lesions in 20% of patients with negative MRI. - MRI-defined FL number was an adverse risk factor for OS on multi-variate analysis.
	Lecouvet, 1999[14]	Symptomatic MM (newly diagnosed)	80	Axial MRI	WBXR	- MRI was normal in 24% of patients, showed focal lesions in 44% and a diffuse pattern in 32% of patients; - WBXR detected lytic bone lesions in 87% of the patients, axial MRI in 79%. - MRI detected spinal or pelvic lesions in 76%. of patients, while WBXR was positive in 46% of patients.
	Mariette, 1999[15]	Asymptomatic myeloma	55	Spinal MRI	WBXR	- BM involvement was detected in 17/55 patients (31%) with a diffuse form in 3, single focal lesion in 6 and multiple focal lesions in 8.
	Baur, 2002[16]	Newly diagnosed MM (active and inactive)	77	Spinal MRI	WBXR	- Twenty (26%) patients with normal-appearing bone marrow of the spine, focal disease in 22 (28%) patients, diffuse pattern found in 24 patients (31%), combined focal and diffuse found in 9 (11%) patients, and salt-and-pepper pattern was found in 2 (3%) patients. - Patients with normal and variegated pattern had a better survival.
WB-MRI	Gleeson, 2009[8]	Newly diagnosed MM (active and inactive)	39	Low-dose CT WB-MRI	WBXR	- CT detected more lesions than WBXR in 71% of patients and results were concordant in 24% of cases. WBXR outscored CT in 5%. - CT resulted in restaging in 25 cases (upstaging in 20, downstaging in 5 cases). - WB-MRI detected more lesions than WBXR or CT in 48% of cases, but CT and WBMRI correlated well in correct staging.
	Ghanem, 2006[17]	MM and MGUS	54	WB-MRI	WBXR	- In 74% patients, WB-MRI and WBXR were concordant, but WB-MRI revealed bone involvement more extensively in 90% of these patients. - In 19% of patients with negative WBXR, WBMRI could detect BM infiltrations and a treatment was started.
	Baur-Melnyk, 2008[18]	Newly diagnosed MM	41	WB-MRI	Low-dose MDCT	- MRI was statistically superior to CT in detecting lesions. - Fifteen patients showed no lesions on both techniques. - Four patients exhibited concordant involvement (focal lesions) in both techniques. - MRI revealed a more extensive disease in 21 patients. - Eleven patients were understaged with CT alone.
	Dinter, 2009[19]	Newly diagnosed (active and inactive)	60	WB-MRI	WBXR	- In 38% of the investigated skeletal regions, WB-MRI revealed additional information such as the degree of bone infiltration or lesions that were not seen on WBXR. - Tumor stage was upgraded in 41 of the 60 patients by the WB-MRI findings.

MM: multiple myeloma; MGUS: monoclonal gammopathy of undetermined significance; WB-MRI: whole-body magnetic resonance imaging; WBXR: skeletal survey by radiographs; CT: computed tomography; PET: positron emission tomography; FL: focal lesion; OS: overall survival.

patients. Treatment-free survival of those sMM patients with MRI images resembling MM patients tended to be shorter compared to patients with an MGUS pattern.[36]

Although BM lesions demonstrated on MRI have a negative prognostic value, there is currently no evidence that these patients require any urgent treatment. These lesions reflect tumor infiltration and not a threat of osteolysis. There is currently no indication that patients who present BM lesions on MRI require treatment. The current interventional trials in sMM include patients with an increased risk of progression, estimated on bone marrow and serum parameters. On the other hand, a closer follow up can be proposed to patients presenting a high risk for progression to symptomatic myeloma in order to avoid major complications.

Summary

- *By definition, WBXR do not show any lytic lesion in patients with smoldering myeloma.*
- *Both axial MRI (spine and pelvis) and WB-MRI are able to demonstrate bone marrow infiltration by MM and have prognostic value. However, results obtained with MRI do not justify the initiation of an anti-myeloma treatment.*
- *There are currently no large studies on the use of PET/CT in this setting.*

Solitary plasmacytoma

The International Myeloma Working Group recommend performing an axial MRI in addition to the skeletal survey.[3] In 1993, Moulopolos assessed the role of MRI in the staging of 12 consecutive patients with a solitary plasmacytoma and found that MRI showed additional foci in one-third of the patients.[39] Due to its ability to identify both medullary and extra-medullary sites of active disease, FDG PET/CT is increasingly being used in the initial workup of patients presenting a solitary plasmacytoma (SP). In several studies, FDG-PET/CT allowed detection of additional bone lesions or soft tissue masses in 30-50% of patients. These findings often changed the ultimate diagnosis and therapeutic decisions, as illustrated in Figure 2.[40-42]

Summary

- *WBXR and axial MRI should be performed in every patient presenting a solitary plasmacytoma in order to exclude other lesions.*
- *If available, PET/CT could be performed in order to detect other medullary or extramedullary lesions. The results obtained with MRI or PET/CT might change the diagnosis and subsequent therapy.*

Active multiple myeloma

Diagnosis

Screening by WBXR or low-dose CT (which is more comfortable for the patient) is mandatory for every patient with a diagnosis of MM. CT has a higher sensitivity compared to WBXR in detecting bone lesions, identifying more lesions in approximately 55% of the patients (mostly located in the axial skeleton). In contrast, WBXR shows more lesions in the skull or appendicular regions in 5% of the patients.[8,43,44] CT is also able to assess the fracture risk and the presence of extramedullary lesions.

Positron emission tomography-CT and MRI showed a higher detection rate than WBXR for bone marrow lesions and small lesions can be found in patients with negative X-ray.[4,11,14,17,29,40,41] Table 1 summarizes the studies on the diagnostic capacities of MRI. The largest study was performed by the Little Rock group and included 668 patients with symptomatic MM. MRI could identify more lesions in the spine, sternum, and pelvis. The authors described that axial MRI was able to detect focal lesions in 52% patients with normal WBXR. CT-guided aspiration of these focal lesions was performed in 125 patients and demonstrated signs of focal osteolysis in 97% of the aspirations.[11] The Bologna group directly compared FDG-PET/CT with WBXR and axial MRI in 46 newly diagnosed symptomatic MM patients.[4] FDG PET/CT proved superior to WBXR in 46% of cases in whom WBXR showed either no lesions or underestimated the extension of bone involvement. In 30% of cases, the results of PET/CT and MRI were discordant, with negative results on PET-CT, but positive MRI. In contrast, 35% of patients presented medullary or extramedullary MM lesions which were detected by PET/CT but which were outside the field of view of MRI. Table 2 illustrates the results on PET/CT in MM.

The accordance between PET/CT and axial MRI was assessed in 4 other studies.[50-52] Three studies confirmed that PET/CT was inferior to MRI in detecting myeloma bone disease, especially in case of diffuse bone marrow infiltration. In the other study, the results were equal.

Summary

- *Screening for osteolytic lesions by WBXR or low-dose CT is mandatory for every patient with MM.*
- *MRI may be considered a complementary examination given its excellent imaging of the axial skeleton and potential identification of spinal cord or nerve root compression.*

Staging and prognosis

Two staging systems are widely used for the staging of MM: the Durie and Salmon staging system and the International Staging System (ISS).[53,54] Because earlier studies could correlate the number of focal bone lesions, the pattern of marrow infiltration seen and the presence of EMD with survival of MM patients, MRI and FDG PET/CT were incorporated in the Durie and Salmon PLUS staging system allowing a better discrimination between patients with stage II from those with stage III disease.[55]

Subsequent studies confirmed the value of MRI and FDG PET/CT to predict patient's outcome at diagnosis.[37,38] The Bologna group recently demonstrated that patients with newly diagnosed MM who presented more than 3 focal lesions, a SUV over 4.2 or an EMD on their diagnostic PET/CT had a poor progression-free survival (PFS).[37] The overall survival (OS) at four years was lower in patients presenting FDG avid lesions (SUV>4.2) or presenting EMD. The presence of EMD at diagnosis and unfavorable cytogenetic abnormalities were independent predictors of shorter time to progression and PFS (Figure 1C and D). These results confirmed an earlier observation made by the Little Rock group that reported a study on the contribution of imaging in treatment response in MM when undergoing the Total Therapy 3 therapeutic program.[38] All patients had a skeletal survey, MRI, and FDG PET/CT at baseline and at specified points in their protocol.[38] The results of the Little Rock study were recently up-dated and showed also a close correlation between the number of focal lesions found by MRI (> 7 lesions) or PET/CT (> 3 lesions) and other biological prognostic factors and gene expression profiling results. Patients with aggressive disease (defined by high-risk gene expression, increased proliferation indices or presence of

centrosome amplifications) had more lesions and higher SUV values.[44] Concerning EMD, the authors found an increased incidence of EMD in patients with a high-risk gene expression profile or cytogenetic abnormalities.[56] The different prognostic studies on PET/CT are summarized in the *Online Supplementary Table S1*.

The prognostic value of the number of focal lesions or the presence of an abnormal pattern on MRI has been evaluated in different studies (summarized in the Online *Supplementary Table S2*). Moulopoulos *et al*. showed that patients with diffuse marrow replacement on MRI had a worse prognosis (median survival of 24 months for patients with a diffuse MRI pattern compared to 56 months in those with a normal pattern).[51] This group also confronted MRI results of 228 newly diagnosed and symptomatic patients with other disease parameters, obtained treatment responses and survival.[13] A diffuse MRI pattern was seen more frequently seen in patients with high-risk cytogenetics and associated with a worse OS compared to other patterns. Combining the diffuse MRI pattern with the ISS score and cytogenetics identified a very high-risk group of patients with a 35% survival rate at three years.[13] The earlier cited study of Walker *et al*. also investigated the prognostic value of MRI and showed a shorter OS of patients with more than 7 lesions compared to those without lesions or with 7 lesions or less.[11] Bartel et al. did not confirm a significant difference in OS according to the number of lesions detected by MRI, but event-free survival was closely correlated with the number of lesions detected (>7 or ≤ 7 lesions).[38]

Summary

- *The results of MRI and FDG PET/CT give prognostic information on both progression-free survival and overall survival.*
- *The presences of more than 3 focal lesions, extramedullary disease and high SUV values on FDG PET/CT have an independent negative prognostic value.*
- *A diffuse infiltration or an increased number (>7) of focal lesions are MR findings associated with a worse prognosis.*

Role of FDG PET/CT and MRI in response assessment

Responses to treatment are measured by well-defined laboratory parameters, but the follow up of bone disease may be more difficult. New or enlarging lesions generally signify disease progression, but lytic lesions rarely show

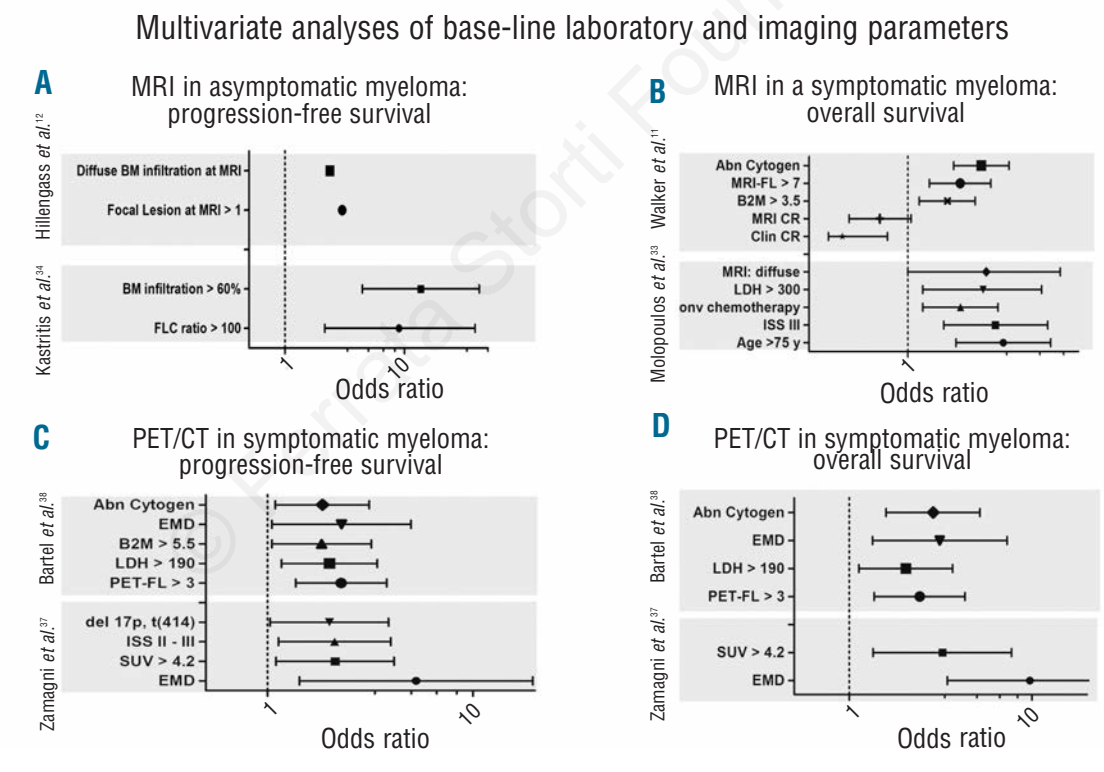

Figure 1. Forest plots of multivariate analyses that included imaging parameters in their variables. (A) In smoldering MM, 2 studies included MRI parameters in the analyzed variables, but in the study of Kastritis *et al*.[34], MRI parameters were no longer significant after multivariate analysis, in contrast to BM infiltration and FLC ratio. Hillengass *et al*.[12] reported the strong prognostic value of the number of focal lesions and the pattern on BM infiltration. (B) For symptomatic MM patients, the study of Milopoulos *et al*.[33] showed that the presence of a diffuse BM infiltration was a negative predictive factor. In the study of Walker *et al*.[11] an increased number (>7) of focal lesions on MRI was associated with a worse survival, while a CR based on MRI criteria was a good prognostic factor. (C) Both studies on PET/CT in symptomatic patients retained the identification of extramedullary disease by PET/CT as a negative prognostic factor for a shorter PFS, while increased SUV values and an elevated number of focal lesions on PET/CT were two other negative prognostic factors. (D) Concerning overall survival, Zamagni *et al.* retained high SUV values and the presence of extramedullary disease as the unique prognostic factors. When gene expression profiling results were omitted, Bartel *et al*.[38] retained the presence of EMD and high numbers of focal lesions as negative prognostic factors. BM: bone marrow; MRI: magnetic resonance imaging; FLC: free light chain ratio; Abn Cytog: abnormal cytogenetics; MRI-FL: number of focal lesions visualized by MRI; B2M: beta-2 microglobulin; MRI CR: complete response, based on MRI findings; EMD: extramedullary disease; LDH: lactate dehydrogenase; PET-F:L number of focal lesions visualized by PET/CT; Clin CR: complete response based on laboratory parameters; ISS: International staging system; SUV: standardized uptake value.

evidence of healing on radiographs. Systematic follow up WBXR is of questionable benefit and not routinely indicated. On the other hand, new vertebral compression fractures do not always signify disease progression and may occur after effective treatment, due to disappearance of the tumor mass that was supporting the bony cortex or due to corticosteroid use during treatment.

Fluorodeoxyglucose PET/CT

Fluorodeoxyglucose PET/CT imaging has been shown to be useful in evaluating response to therapy and to have prognostic significance. Patients appear to have a poor prognosis if abnormal FDG uptake is still present following high-dose therapy or SCT. The Bologna group evaluated the FDG PET/CT in 2 prospective studies. Their second study included 192 patients treated by an induction treatment (thalidomide/dexamethasone) and autologous stem cell transplantation (ASCT).[37] Persistent FDG-avid lesions after induction were predictive of a shorter OS and PFS, while negativity for hypermetabolic lesion on FDG PET/CT performed three months after ASCT was associated with a favorable outcome. On multivariate analysis, incomplete FDG suppression after ASCT was strongly associated with a worse PFS and OS (HR: 3.90). A very good partial response (VGPR) was observed in 95% of patients with a negative PET after ASCT. Importantly, 23% of patient who achieved a biological complete remission had still positive PET lesions, which was associated with a worse outcome (PFS at 4 years was 30% for patients in CR with persistent hypermetabolism *vs.* 61% for patients in complete biological and metabolic response).[37]

The Little Rock group had earlier demonstrated that complete metabolic response of focal lesions and metastatic spread before transplantation conferred superior OS and EFS.[38] This group recently reported the prognostic value of early PET/CT (performed at Day 7 of the induction treatment). Three-year OS and PFS estimates for patients presenting more than 3 focal lesions were 63% and 56% compared to 78% and 82% for patients with 1-3 lesions.[58]

The results obtained from the Little Rock and Bologna Studies suggest that PET results after ASCT could be incorporated into the response criteria for CR as well as for persistent disease. However, confirmation by other large clinical trials, such as the IFM/DFCI trial and the European Myeloma Network trial, are needed before PET/CT can be recommended in this setting. The Bologna and Little Rock studies included patients who were treated with ASCT. Data on treatment response in patients ineligible for transplant are limited and, therefore, the use of PET/CT in assessment of disease response can only be proposed to transplant-eligible patients.

Table 2. Diagnostic studies on FDG PET and FDG PET/CT.

	Author (ref)	Patients	N.	Examinations	Key findings
FDG PET	Schirmeister, 2002[41]	Prospective study on MM and plasmacytoma.	43	FDG PET *vs.* WBXR, MRI and CT	- PET and WBXR were concordant in 34% (38/112). - WBXR was superior to PET in 3% (3/112). - PET superior to WBXR in 63% (71/112).
	Adam, 2007[45]	Prospective study on MGUS, MM and plasmacytoma.	49	FDG PET *vs.* WBXR and MRI	In MM: WBXR and PET concordant in 76% (10/13). PET superior to WBXR in 24% (3/13).
	Hur, 2008[46]	Retrospective study on newly diagnosed MM.	22	FDG PET and axial MRI	In SD stage I and II, FDG PET and MRI were not statistically different for the detection of bone lesions. In SD stage III: MRI was statistically superior to FDG PET in detecting lesions.
FDG PET/CT	Waheed, 2012[44]	Retrospective study on newly diagnosed patients with symptomatic MM.	270	WBXR *vs.* FDG PET/CT and MRI	- Results of MRI and PET were similar, but superior to WBXR. - A strong correlation between laboratory values (β2-microglobin, CRP, LDH) and gene expression derived variables and the number of focal lesions and PET/CT SUV.
	Zamagni, 2007[4]	Prospective study on symptomatic newly diagnosed MM.	46	WBXR *vs.* FDG PET/CT Axial MRI *vs.* FDG PET/CT	- WBXR and PET/CT were concordant in 46% (21/46). - WBXR was superior to PET/CT in 8% (4/46). - PET/CT superior to WBXR in 46% (21/46). - MRI and PET/CT were concordant in 70% (32/46). - MRI superior to PET/CT in 30% (14/46).
	Salaun, 2008[47]	Retrospective study on plasmacytoma.	24	FDG PET/CT and WB MRI	- MRI and PET/CT concordant for 60% (12/20) of the lesions; - PET/CT detected plasmacytoma lesions in 10/20 patients (50%), which were outside the scope of MRI.
	Shortt, 2009[48]	Retrospective study on MM.	24	FDG PET/CT and WB-MRI	PET and whole-body MRI findings were concordant in 62% of cases (21/34). In discordant cases. (13/21), WBMRI correctly diagnosed 8/13 cases.
	Sager, 2011[49]	Retrospective study on MM.	42	FDG PET/CT *vs.* WBXR	In patients with newly diagnosed MM (n=32), FDG PET showed sensitivity of 90% *vs.* 84% for the conventional techniques. For all patients, mean SUVmax was 5.21 (ranging from 1.0 to 14.5) and was significantly correlated with plasma cell infiltration.
	Spinnato, 2012[50]	Retrospective study at different stages of MM disease	191	FDG PET/CT and Axial MRI	At diagnosis, PET/CT failed to detect diffuse BM involvement in 9/62 patients (14%). In 37% of patients, PET/CT allowed the detection of lesions outside the field of view of MRI. Post-treatment PET/CT was negative in 38/40 patients (95%) who achieved excellent responses whereas MRI showed active disease in 27/ 40 patients.

MM: multiple myeloma; MGUS: monoclonal gammopathy of undetermined significance; WB-MRI: whole-body magnetic resonance imaging; WBXR: skeletal survey by radiographs; CT: computed tomography; PET: positron emission tomography; FL: focal lesion, SD: Salmon and Durie.

Magnetic resonance imaging

While MRI is a powerful tool to detect marrow lesions, its use for the assessment of response to treatment has limitations. When a MM marrow lesion responds to treatment, red marrow replaces the tumor tissue and fatty yellow marrow appears only several months later. This implies that the pattern of BM infiltration on T1- and T2-weighted MR images may not change early after induction chemotherapy and an interval of three months has been suggested before MRI monitoring.[59] The Heidelberg group recently published a retrospective study on the correlation between responses assessed by laboratory analysis and by changes in MRI.[60] When MRI showed a diffuse infiltration, laboratory results correlated well with MRI changes. In addition, the authors reported that persisting focal lesions on MRI after ASCT was associated with an inferior OS and PFS (patients with >10 focal lesions had a survival rate of 64% at 2 years compared to 100% for patients without focal lesions).[60] Another prospective study included 33 patients treated with ASCT.[61] MRI and serum analyses agreed in 26 out of 33 patients (78.8%) on the obtained responses. WBMRI was classified as false positive in 3 patients and false negative in 4 patients. Statistical analysis found moderate concordance between laboratory and MRI evaluation of disease evolution.[61] Functional MRI techniques such as dynamic contrast-enhanced MRI can be of additional value; a study on pre- and post-treatment DCE MRI confirmed that patients with a good clinical response had a lower increase and another pattern of contrast enhancement (a delay in peak enhancement *vs.* early enhancement before treatment) compared to poor responders.[59]

Fluorodeoxyglucose PET/CT versus magnetic resonance imaging for assessment of treatment response

Fluorodeoxyglucose PET/CT and WB-MRI were recently compared in a prospective study evaluating treatment responses in 31 patients treated with ASCT.[61] Comparison of the imaging results with laboratory response criteria showed that PET/CT had a sensitivity of 50% and a specificity of 85% compared to standard criteria, while MRI had a sensitivity of 80% and a specificity of only 38%. MRI was often falsely positive because of persistent non-viable lesions. The remission status determined by FDG PET/CT (and not by MRI) was significantly correlated with the results of the standard response criteria.[62]

Summary

- *Two large prospective studies confirmed the prognostic value of FDG PET/CT results after induction treatment and after ASCT in transplant-eligible patients.*
- *In this setting, incomplete FGD suppression is associated with a worse overall and progression-free survival.*
- *MRI may be useful for the follow up of diffuse BM infiltration. Focal lesions may remain hyperintense, and the correlation with biological responses is only weak.*

Current issues in imaging

Modern imaging techniques such as MRI and FDG PET/CT are reliable tools in the determination of diagnosis and prognosis of MM patients. These techniques should be included in upcoming clinical trials to confirm their prognostic value and to guide treatment changes currently tested in lymphoma.

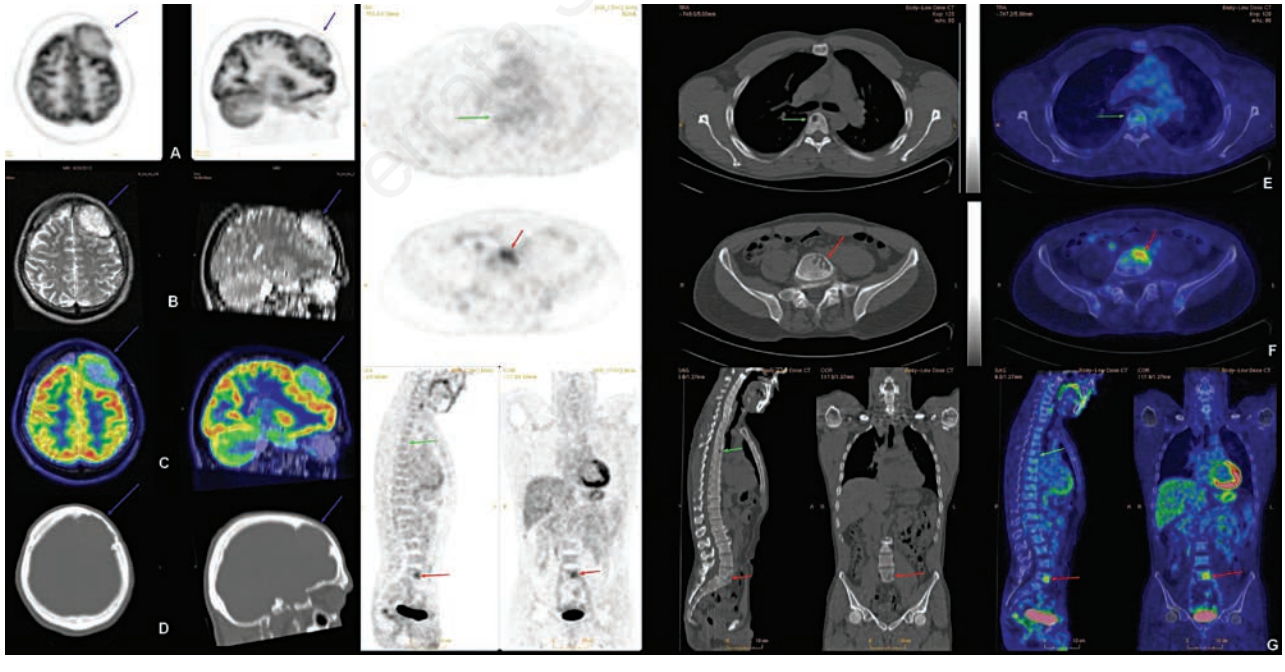

Figure 2. A 48-year old patient consulted for a monoclonal gammopathy. The whole body skeletal survey showed a unique extensive bone lesion in the left frontal bone of the skull and no other bone lesion was found. Bone marrow aspirate showed a plasmacytosis of 2%. On FDG PET/CT images (A: FDG PET; B: MRI; C: fused FDG PET/MRI; D: the low dose CT of the PET), the skull lesion (blue arrows) showed a high FDG uptake with a SUVmax estimated at 10.51. On the whole body FDG PET/CT images, additional lytic bone lesions were detected including one FDG-avid in the 5th lumbar vertebra (red arrows; SUVmax 3.76). The green arrows show a lytic bone lesion with no FDG uptake in the 6th dorsal vertebra.

In general, WBXR remains the test of choice to detect osteolytic lesions, but it could be replaced by WBCT that is more sensitive for lesions located in the spine, pelvis or thoracic cage.

In symptomatic myeloma, both MRI and FDG PET/CT are currently exploited as additional diagnostic tools. A systematic review on imaging techniques in myeloma indicated that the detection capabilities of MRI outscore the results obtained with CT or PET/CT.[22] However, MRI is of limited value in the assessment of disease response after therapy. For transplant-eligible patients, FDG PET/CT is superior for re-evaluating myeloma disease after induction treatment and ASCT, and 2 large prospective studies validated the prognostic value of extramedullary disease and residual hypermetabolic activity after treatment. One could state that MRI and FDG PET/CT may have complementary roles in disease assessment, because MRI is excellent in recognizing myeloma infiltration in the axial skeleton at diagnosis, while FDG PET/CT can be used in the assessment of treatment response.

Fluorodeoxyglucose PET/CT may also have a role in the assessment of minimal residual disease. This is currently being evaluated by multiparameter flow cytometry or by a specific polymerase chain reaction. The latter remains a difficult assay to perform, as it requires the generation of patient-specific primers. In flow cytometry, the quantification of residual myeloma cells requires sophisticated analyses, but once the technique is automated, it gives objective results. Both techniques are unable to detect extramedullary disease, which is now being observed more frequently at time of relapse after novel therapies. FDG PET/CT scan may be of additional value for the detection of both extramedullary and medullary minimal residual disease.

However, further use of these techniques in daily practice requires standardization in the interpretation and reporting. For FDG PET/CT, the number of focal lesions and the intensity of FDG uptake should be taken into account. In parallel to the development of PERCIST criteria, the use of the SUV peak (mean SUV obtained in a 1 cm^3 sphere centered on the voxel of maximum activity concentration) could be a more robust quantitative parameter.[28] For MRI, a number of 7 lesions has been proposed as a significant prognostic parameter when axial MRI is used. For WB-MRI, no distinct cut off has been published and this should be studied. The results of functional MRI (dynamic contrast-enhanced and diffusion-weighted imaging) need to be further validated and hybrid PET/MRI could become a promising tool combining MRI and PET in one single examination.

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