Guidelines of the Belgian Hematology Society for imaging in multiple myeloma

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SUMMARY

Despite major improvements in the diagnosis and treatment of multiple myeloma (MM), bone damage remains a major feature of this disease. With the development of new diagnostic tools, conventional skeletal studies have been progressively replaced by novel imaging techniques. Today, imaging plays a crucial role in defining symptomatic multiple myeloma, measurement of the extent of skeletal involvement and assessing therapeutic response including minimal residual disease (MRD). Based on an extensive review of the recent literature, we propose an array of Belgian recommendations for myeloma imaging to be used as a reference by haematologists in their daily practice.

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INTRODUCTION

MM is a malignant plasma cell disorder of post-germinal center B-cells characterised by the expansion of clonal plasma cells (PCs) in the bone marrow (BM).[1] MM is associated with a variety of clinical manifestations but the most common symptoms at diagnosis are bone pain and fatigue.[1] Approximately 75% of the patients present with skeletal abnormalities on their initial evaluation and up to 90% will develop lytic bone lesions during the evolution of their disease.[2] During the last two decades, major advances have been made in the treatment of MM, but also in newer diagnostic tools used to stage the disease and assess the extent of the bone damage. Depending on the imaging technique used, different pathological anomalies can be found on investigation such as osteolysis, fractures, bone lesions, focal lesions, diffuse infiltration, plasmacytoma, nerve or spinal cord compressions, extramedullary disease (EMD), osteoporosis and osteosclerosis.

Imaging plays an important role in evaluating the disease upon diagnosis, in guiding biopsy, in deciding to perform radiotherapy or surgery and in evaluating response to treatment or relapse. The role of imaging has become even more crucial in the decision to treat after the publication of new definition of symptomatic MM.[3]

IMAGING UPON DIAGNOSIS

ROLE OF CONVENTIONAL RADIOGRAPHY

In 1975, Durie reported that lesions detected by conventional X-ray were correlated with the tumour burden of MM patients and until recently, whole-body skeletal

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TABLE 1. WBXR in MM patients.

Advantages	Disadvantages
Availability	Low sensitivity in anatomically complex regions (pelvis and spine)
Good sensitivity in appendicular skeleton, ribs and skull	Low specificity for distinguishing benign lesions or fractures especially in the context of osteoporosis
Evaluation of fractures or risk for fracture especially in the appendicular skeleton	Observer-dependent
Low cost	Difficult to perform with patients with severe pain

TABLE 2. WBLDCT in MM patients.

Advantages	Disadvantages
High sensitivity for the detection of osteolytic lesions and for the assessment of fracture risk (especially in the spine and pelvis)	Underestimation of diffuse bone marrow disease
No need for contrast administration	No information on the activity of the lesions
Use of low-dose protocol compared to standard CT exams	Limited role in response assessment
Higher comfort in patients with bone pain, faster than CR and no need for repositioning of the patient.	
Three-dimensional and multidirectional images can be reconstructed to evaluate bone instability and for planning interventional procedures	
Provide information on the bone matrix (e.g. osteoporosis)	
Reveals unexpected findings (e.g. tumoural lesions in the lung or abdominal masses) and EMD	

X-ray (WBXR) was recommended as the standard method for the evaluation of osteolysis at initial diagnosis.[4] The WBXR mostly detects osteolysis but also a combination of osteolysis, osteopenia and fractures.[5] Osteolytic lesions will typically present as punched-out lesions without reactive sclerosis. Although WBXR has been widely used for bone evaluation and retains a good sensitivity in some anatomical regions such as the appendicular skeleton, ribs and skull, this technique has several limitations. Osteolytic lesions are only detected when a minimum of 30% trabecular bone is destroyed but this could possibly rise up to 50-75%, resulting in an under-estimation of bone damage in 25-45% of the cases.[6-8] WBXR potentially misses bone lesions, particularly in anatomically complex regions such as the axial skeleton, pelvis and in patients with reduced bone density.[6,9] In addition, detection of bone involvement is observer-dependent, indicating that x-rays should be reviewed by a musculoskeletal radiologist.[6] Moreover, WB assessment can be difficult to perform with patients in severe pain.[10]

ROLE OF COMPUTERISED TOMOGRAPHY IN MM PATIENTS

Criteria for the diagnosis of bone disease in MM have been redefined by the International Myeloma Working Group (IMWG), using new imaging techniques.[3,11] MM bone disease includes the presence of at least one osteolytic bone lesion of ≥ 5 mm, not only assessed by x-rays but also by conventional CT or whole-body low-dose CT (WBLDCT) or PET-CT.

Several authors have shown the superiority of WBLDCT over WBXR for the detection of myeloma bone disease.[12,13] A large imaging study demonstrated that 61% of patients with a normal skeletal survey showed at least one or more osteolytic bone lesions with WBLDCT. WBLDCT has replaced WBXR and should be used at the time of diagnosis for evaluating the presence, size, localisation and number of osteolytic lesions or fractures in MM patients.[9] In addition, this technique allows the detection of lesions at risk for pathological fracture requiring immediate intervention (radiation, surgery). It has also been reported

TABLE 3. MRI in MM patients.

Advantages	Disadvantages
Highest sensitivity for detecting bone marrow involvement compared to other techniques	Cost
Allows to distinguish benign fractures related to osteoporosis from fractures related to osteolysis	Limitation of use in patients with • severe pain (timing of acquisition) • claustrophobia
Procedure of choice to evaluate nerve or cord compression	Contra-indication in patients with MRI-incompatible implants, pacemakers…
Can detect focal lesions in SMM, allowing for the restaging of patients (based on the presence of myeloma-defining events), thereby fulfilling the criteria for treatment	Limited role in response assessment
High sensitivity for the detection of bone lesions upon diagnosis	No information on the activity of lesions unless DWI or DCE techniques are used
No radiation exposure	Availability and waiting lists
Can reveal unexpected findings (e.g. tumoural lesions in the lung or abdominal masses) and EMD	
Prognostic value upon diagnosis	
Assessment of disease extension in solitary plasmacytoma	

TABLE 4. FDG-PET/CT in MM patients.

Advantages	Disadvantages
High sensitivity for the detection of bone lesions upon diagnosis	Cost
Prognostic value upon diagnosis (e.g. high SUV index, number of focal lesions, presence of EMD)	Could miss small lytic lesions
Prognostic value at the end of treatment (persistence of FDG avidity in patients even in CRs)	Less sensitive than MRI to detect diffuse marrow involvement
Assessment of therapeutic response and minimal residual disease	Possible false positive: • in inflammation or infection areas • post-surgery or radiotherapy • in other malignant processes • due to use of growth factors
Evaluation and follow-up of non- or oligo- secretory MM	Possible false negative: • in hyperglycaemia • with recent use of high dose steroids • due to low expression of hexoquinase-2
Identification of unexpected findings (e.g. tumoural lesions in the lung or abdominal masses) and EMD	
Assessment of disease extension in solitary plasmacytoma	

that in patients with smoldering MM (SMM), WBLDTCT detects osteolytic lesions in about 22% of patients with negative conventional radiography.[14]

ROLE OF MRI IN MM PATIENTS

MRI is the only imaging technique that allows for the direct visualisation of bone marrow tissue with high spatial resolution. When compared to other imaging techniques such as WBXR and WBLDCT, whole body MRI (WBMRI) possesses the highest sensitivity and specificity for the detection of bone marrow infiltration.[15,16] This high sensitivity enables MRI to detect bone marrow infiltration before the destruction of mineralised bone, thus before the occurrence of osteolysis.[15,17] In MM, five different patterns of infiltration have been identified, *i.e.* normal

appearing marrow, focal infiltration, diffuse disease, salt-and-pepper pattern and combined infiltration pattern.[18] Also, MRI can depict epidural expansion of myeloma tissue, identifying patients at risk for spinal cord compression.[19] Conventional MRI-imaging in the work-up of plasma cell disorders also offers the advantages of being widely available with no radiation exposure for the patient. The addition of functional MRI imaging techniques, such as dynamic contrast enhanced (DCE-MRI) and diffusion weighted imaging (DWI-MRI) can improve the detection rate of MRI.[16,19,20]

In smoldering MM (SMM), MRI allows the detection of focal lesions (FLs). In the presence of more than one FL (more than 5 mm), the patient meets one of the three so-called "myeloma-defining events".[3] In addition, the presence of either a diffuse bone marrow infiltration pattern or an increase in number or size of focal lesions has also been shown to have prognostic value, leading to the recommendation of performing follow-up examinations within a timeframe of three to six months in patients with these lesions.[3] In symptomatic MM patients, MRI, compared to conventional WBXR, provides a higher detection rate of MM-related bone disease.[13,19] Although both WBMRI and MRI confined to the axial skeleton (spine and pelvis) outperform WBXR, a direct comparison of both techniques revealed that approximately 10% of patients show lesions exclusively outside of the axial skeleton.[21] As such, MRI of the axial skeleton and pelvis should be used when no WBMRI is available. MRI is also relevant in newly diagnosed MM (NDMM) patients as the presence of more than seven lesions in spinal MRI have been reported to be an adverse prognostic factor. Additionally, MRI can differentiate normal from pathological bone marrow, helping us distinguish pathological compression fractures from benign osteoporotic ones.[13,19]

In patients with solitary plasmacytoma of the bone (SPB), it is very important to exclude other bone marrow lesions that cannot be seen on WBXR, since extended bone involvement is associated with a high risk of progression to MM, and treatment with radiotherapy alone might not be appropriate. Therefore, WBMRI should be used in patients with suspected SPB in order to assess the extent of the disease and rule out other focal lesions.[11]

However, MRI is associated with drawbacks that limit its use in certain patient groups. It has a higher cost when compared to other imaging techniques. The scanning time is relatively long, a fact that precludes its use in severely ill patients.[11] In addition, this imaging tool cannot be offered to patients suffering from claustrophobia or those with MRI-incompatible implants.

THE ROLE OF FDG-PET/CT IN MM PATIENTS

In MM, FDG-PET/CT yields highly sensitive detection of malignant bone marrow infiltration, EMD and functional information.[22] The simultaneously performed LDCT allows an evaluation of MM-related bone disease. However, some limitations should be noted regarding the use of this technique in MM. Hyperglycaemia resulting from the concomitant use of high dose corticosteroids will compete with fluorodeoxyglucose (FDG) for tumour cell entry, thereby reducing FDG uptake. In addition, FDG is not tumour specific, and tissue inflammation (*e.g.* recent radiotherapy, surgery, chemotherapy, infection, fracture) or the use of growth factors can induce false positive results.[23] False negative results could be related to a low expression of hexokinase-2 in 10-15% of the patients.[24]

FDG-PET/CT performed at MM diagnosis allows a sensitive assessment of myeloma bone disease (lytic bone lesions and fractures) based on CT, and an evaluation of EMD and bone marrow based on PET. This technique is more sensitive than WBXR for the detection of lytic bone lesions. Furthermore, as FDG-PET/CT is of distinct value in the follow-up of MM patients, a baseline exam serves as an excellent comparison tool for subsequent imaging performed for the assessment of the treatment response. Several studies support the notion that FDG-PET/CT in NDMM has a prognostic value either upon diagnosis, at predefined time-points during treatment or as a tool for treatment response assessment.[25,26] Different trials demonstrated the negative impact of the presence of more than three FDG-avid focal lesions and the presence of EMD in NDMM on PFS and OS.[26-28] Additionally, reaching FDG-PET/CT negativity pre- or post-ASCT conferred superior PFS and OS in comparison to those that remained positive.[28,29]

These results led the IMWG to propose a definition for FDG-PET/CT imaging response as either the disappearance of every area of increased tracer uptake found at baseline or on a previous FDG-PET/CT, a decrease to less than the mediastinal blood pool SUV, or a decrease to less than that of surrounding normal tissue (*i.e.* Deauville score of one or two).[30]

Even though MM is a mostly widespread systemic disease, a minority of patients (3%) will present with a solitary bone lesion or SPB. Adequately assessing a localised plasma cell tumour from its systemic counterpart is of major importance since localised diseases are usually treated with radiotherapy alone. FDG-PET/CT has been shown to sensitively identify other disease localisations, upgrading previously thought localised diseases to MM status.[31,11]

TABLE 5. Recommendations for imaging in MM patients.

	Recommendations	If first evaluation negative	If not available or contraindicated	Follow-up and remarks
Solitary plasmacytoma	• WBMRI Or MRI spine – pelvis if WB-MRI not available (level 5) • FDG-PET/CT in newly diagnosed EMD plasmacytoma (level 4)		FDG-PET/CT (level 5)	Repeat at least 1x year for 5 years
SMM	WBXR no more a standard (level 4) WB – CT (level 3)	WB MRI or MRI spine – pelvis if not available (level 4)	FDG-PET/CT (level 4)	Repeat at least 1x year for 5 years (level 5)
MM at diagnosis	WBXR no more a standard (level 3) WB – CT (level 3) or FDG-PET/CT (level 4)	WBMRI (level 4)	MRI of pelvis axial skeleton + conventional X-Ray of the appendicular skeleton (level 4)	Pet allows for MRD assessment
Suspicion of spinal compression	Emergency MRI		Emergency CT	
MM response assessment	FDG-PET/CT		WBDWI-MRI if performed at diagnosis	Repeat Pet 1x year for 5 years in patients with residual lesions (HR of early progression) (level 5)
Relapse	• Redo same investigation done at baseline • WBCT if WBXR performed at diagnosis (level 5)			

Recommendations based on the IMWG 2019 recommendations on imaging in plasma cell dyscrasia.[11]

IMAGING IN THE POST-TREATMENT SETTING

IMAGING DURING FOLLOW-UP

The IMWG recommends yearly follow-up imaging only in patients with residual lesions detected by FDG-PET/CT due to the high risk of early progression.[11] In other patients, there are no indications to perform additional skeletal studies during follow-up unless the patient develops progressive disease or bone symptoms. However, FDG-PET/CT is of relevant clinical value in the follow-up of non- or oligo-secretory MM.[11]

IMAGING UPON RELAPSE

At the time of relapse, imaging techniques used upon diagnosis should be repeated. They allow the assessment of the evolution of pre-existing lesions and the detection of new ones.[11] WBXR is not the best technique to be performed upon relapse but could help in detecting lesions at risk of fracture.

If WBXR has been performed upon diagnosis, WBLDCT should be performed to assess the extent of bone destruction.[11]

LIST OF ABBREVIATIONS	
CR	Conventional Radiography
CT	Computerised Tomography
EMD	Extramedullary Disease
FDG	Fluorine Deoxy-Glucose
IMWG	International Myeloma Working Group
PET-CT	Positron Emitting Tomography – Computerised Tomography
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
WB	Whole-Body
WBLDCT	Whole-Body Low-Dose Computerised Tomography
WBMRI	Whole-Body Magnetic Resonance Imaging
WBXR	Whole-Body X-Rays

CONCLUSIONS AND RECOMMENDATIONS

WBXR is no longer the gold standard and should be replaced by cross-sectional imaging technics (level 4).

WBLDCT should be used for the evaluation of lytic bone lesions (level 3) and could be replaced by FDG-PET/CT (level 4).

If WBLDCT or FDG-PET/CT are negative additional WBMRI, or at least spine plus pelvis MRI must be performed to exclude focal lesions as MDE (level 4).

In case of a suspicion of spinal cord or nerve compression, an emergency MRI is the imaging technique of choice. If an MRI is not rapidly available or contra-indicated, an emergency CT must be performed.

MRI should be used to differentiate benign (mostly osteoporotic) from MM-related vertebral fractures.

In SMM with no bone involvement as assessed by WBLDCT, a WBMRI should be performed in order to detect focal lesions (level 3).

Solitary plasmacytoma assessment should include WBMRI to exclude other focal lesions that imply the need for a systemic therapy (level5). If WBMRI is not available FDG-PET/CT is an adequate alternative (level 5). FDG-PET/CT is recommended at diagnosis (level 4) and should be repeated yearly for at least five years (level 5).

FDG-PET/CT is the best imaging technique to assess treatment response (level 4).

MRI before treatment and FDG-PET/CT before and after treatment have prognostic value but do not currently have any impact on treatment decisions.

REFERENCES

1. Palumbo A, Anderson K. N Engl J Med. 2011;364(11):1046-60.
2. Melton LJ III, Kyle RA, Achenbach SJ, et al. J Bone Miner Res. 2005;20(3):487-93.
3. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. Lancet Oncol. 2014;15(12): e538-48.
4. Durie BG, Salmon SE. Cancer. 1975;36(3):842-54.
5. Terpos E, Dimopoulos MA. Ann Oncol. 2005;16(8):1223-31.
6. Kröpil P, Fenk R, Fritz LB, et al. Eur Radiol. 2008;18(1):51-8.
7. Dimopoulos M, Terpos E, Comenzo RL, et al. Leukemia. 2009;23(9):1545-56.
8. Hipp JA, Springfield DS, Hayes WC. Clin Orthop Relat Res. 1995;(312):120-35.
9. Princewill K, Kyere S, Awan O, et al. Cancer Invest. 2013;31(3):206-11.
10. Singh J, Fairbairn KJ, Williams C, et al. Br J Haematol. 2007;137(2):172-3.
11. Hillengass J, Usmani S, Rajkumar SV, et al. Lancet Oncol. 2019;20(6):e302-e312.
12. Gleeson TG, Moriarty J, Shortt CP, et al. Skeletal Radiol. 2009;38(3):225-36.
13. Regelink JC, Minnema MC, Terpos E, et al. Br J Hematol. 2013;162(1):50-61.
14. Horger M, Claussen CD, Bross-Bach U, et al. Eur J Radiol. 2005;54(2):289-97.
15. Hillengass J, Landgren O. 2013;54(7):1355-63.
16. Mesguich C, Hulin C, Latrabe V, et al. Ann Hematol. 2020;99(12):2869-80.
17. Schmidt G, Reiser M, Baur-Melnyk A. Eur J Radiol. 2009;70(3):393-400.
18. Alyas F, Saifuddin A, Connell D. Diagn Interv Radiol. 2013;19(5):393-9.
19. Caers J, Withofs N, Hillengass J, et al. Haematologica. 2014;99(4):629-37.
20. Dutoit J, Vanderkerken M, Verstraete K. Eur J Radiol. 2013;82(9):1444-52.
21. Bäuerle T, Hillengass J, Fechtner K, et al. Radiology. 2009;252(2):477-85.
22. Usmani SZ, Heuck C, Mitchell A, et al. Haematologica. 2012;97(11):1761-7.
23. Zamagni E, Tacchetti P, Cavo M. Blood. 2019;133(7):644-51.
24. Juweid ME, Cheson BD. N Engl J Med. 2006;354(5):496-507.
25. Kumar S, Paiva B, Anderson KC, et al. Lancet Oncol. 2016;17(8):e328-e346.
26. Usmani SZ, Mitchell A, Waheed S, et al. Blood. 2013;121(10):1819-23.
27. Zamagni E, Patriarca F, Nanni C, et al. Blood. 2011;118(23):5989-95.
28. Zamagni E, Nanni C, Mancuso K, et al. Clin Cancer Res. 2015;21(19):4384-90.
29. Moreau P, Attal M, Karlin L, et al. Blood. 2015;126(23):395.
30. Zamagni E, Nanni C, Dozza L, et al. J Clin Oncol. 2021;39(2):116-25.
31. Nanni C, Rubello D, Zamagni E, et al. In Vivo. 2008;22(4):513-7.