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REVIEW ARTICLE

From standard radiography to whole-body MRI: 30 years of progress in multiple myeloma imaging

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ABSTRACT

Multiple myeloma (MM) is a hematologic cancer characterized by clonal proliferation of plasma cells within the bone marrow. It is the most serious form of plasma cell dyscrasias, whose complications—hypercalcemia, renal failure, anemia, and lytic bone lesions—are severe and justify the therapeutic management. Imaging of bone lesions is a cardinal element in the diagnosis, staging, study of response to therapy, and prognostic evaluation of patients with MM. Historically, the skeletal radiographic workup (SRW), covering the entire axial skeleton, has been used to detect bone lesions. Over time, new imaging techniques that are more powerful than SRW have been evaluated. Low-dose and whole-body computed tomography (CT) supplants SRW for the detection of bone involvement, but is of limited value in assessing therapeutic response. Bone marrow MRI, initially studying the axial pelvic-spinal skeleton and more recently the whole body, is an attractive alternative. Beyond its non-irradiating character, its sensitivity for the detection of marrow damage, its capacity to evaluate the therapeutic response and its prognostic value has been demonstrated. This well-established technique has been incorporated into disease staging systems by many health systems and scientific authorities. Along with positron emission tomography (PET)-18 fluorodeoxyglucose CT, it constitutes the current imaging of choice for MM. This article illustrates the progress of the MRI technique over the past three decades and situates its role in the management of patients with MM.

Keywords: Myeloma; Bone Marrow; Imaging; MRI; Cancer

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1. The disease, its staging, imaging

Multiple myeloma (MM) or Kahler's disease is the most severe disease of the plasma cell dyscrasias (or monoclonal gammopathies), which characterized by the uncontrolled proliferation and accumulation within the bone marrow of tumor plasmacytes, resulting in the existence of a serum monoclonal compound (para-protein, immunoglobulin, or immunoglobulin fragment). The disease progresses from an asymptomatic pre-cancerous stage, monoclonal gammopathies of undetermined signification (MGUS), to a stage of "latent" or indolent multiple myeloma (smoldering multiple myeloma in English (SMM)) and finally to the stage of symptomatic myeloma, characterized by the severity of its repercussions[1,2]. The definition of symptomatic MM, the most severe entity of plasma cell dyscrasias requiring therapeutic management, is based on the presence of an abnormal plasma cell lineage representing more than 10% of the bone marrow cellularity and the existence of "organ damage" related to plasma cell infiltration, and defined by the "CRAB" criteria: presence of hypercalcemia, renal insufficiency, ane-

mia, or bone damage. This definition was revised in 2014 by the "International Myeloma Working Group" (IMWG), incorporating new biomarkers with the primary aim of recognizing high-risk indolent myeloma, in order to avoid delay in treatment and the development of bone lesions at risk of complications or renal insufficiency[1]. These biomarkers, defining an 80% probability of progression from indolent myeloma to symptomatic myeloma with CRAB criteria, are the existence of a medullary clone of abnormal plasma cells with J plasmacytosis at 60%, a serum free light chain (monoclonal)/J involved light chain ratio at 100, or the existence of more than one focal lesion larger than 5 mm in diameter on MRI or CT.

Bone imaging plays a cardinal role in the management of the disease, and is integrated into the initial diagnostic approach, staging, and initiation of treatment of MM. MM is in fact characterized by the existence of osteolytic bone lesions, which cause frequent complications[3]. In addition, imaging has a prognostic role, both in advanced forms requiring therapeutic management, and in indolent monoclonal gammopathies and myelomas, where it is expected to recognize subpopulations of patients with a pejorative evolutionary risk[4-6]. For more than 40 years, staging systems have existed to stratify the disease and the therapeutic approach.

The staging of Durie and Salmon, introduced in 1975, distinguishes three stages based on biological tests and the existence of lytic lesions detected by the "skeletal radiographic workup" (SRW), which has been the imaging of choice in MM since that time[7]. The development of biological tools and the demonstration of their prognostic value led to the emergence of new staging systems: the "International Staging System" (ISS), introduced in 2005, distinguishes three categories of MM patients based solely on two biological parameters: serum beta-2-microglobulin and serum albumin[8]. This ISS has been revised (R-ISS), adding to these two parameters the serum LDH value and the absence or existence of chromosomal abnormalities (17p deletion and/or translocation[4,9] and/or translocation[9-11].

At the same time, the perception of the limitations of SRW and the advent of new imaging techniques, which are more effective in detecting bone involvement, have led to the development of staging systems incorporating these "modern techniques"—magnetic resonance imaging (MRI) and positron emission tomography (PET)—computed tomography (CT). Durie and Salmon's "PLUS" staging, which appeared in 2006, relies solely on the detection of bone marrow lesions by these two techniques[12].

More recently, the superiority of whole-body MRI over SRW and its prognostic value have led to its promotion "as first-line imaging" in the development of a suspected myeloma patient, notably in the United Kingdom[11,13].

2. Imaging techniques and detection of bone damage in the MM

2.1 The skeletal radiographic workup (SRW)

SRW studying the skull, spine, ribs, humeri, and femurs has been the method routinely used since 1975 for the detection of osteolytic plasma cell foci typical of MM[14]. More than 80% of patients with MM suffer destructive bone lesions that can cause fractures, pain, neurological deficit, and impaired quality of life[3]. Histological analyses show the existence of bone destruction phenomena adjacent to tumor plasma cells, combined with severe inhibition of bone formation[15]. Without going into details, the medullary infiltration by plasma cells is accompanied by the secretion of factors stimulating osteoclastic proliferation, leading to bone resorption which in turn favors plasma cell proliferation in a vicious cycle of bone destruction and tumor progression. Cytokines are also responsible for a profound inhibition of osteoblastic activity and apoptosis of osteoblasts[9,16].

The radiating and expensive SRW includes lateral views of the skull, spine, and front of the humeri, ribs, and femurs; some add frontal radiographs of the skull and spine. The SRW is obtained for the purpose of categorizing patients according to the staging of Durie and Salmon. The detection of "advanced osteolytic lesions" (concretely, more than one centimetric lesion) signals the severity of the disease (stage 3), requiring therapeutic management. The lesions observed are typically lytic,

well delimited, “cookie cutter”, without peripheral sclerosis. In the case of a single lytic lesion, and in the absence of abnormalities on bone marrow aspiration and protein electrophoresis, the diagnosis of solitary plasmacytoma is accepted. Other frequent radiographic findings are diffuse osteoporosis, more or less inhomogene, pathologic fractures, and in particular vertebral settlements that may be related to local embrittlement by a focus of osteolysis, or to the diffuse osteopenia accompanying the disease[10].

The diagnostic value of SRW is highly imperfect. Performing well at the height of flat bones, with a high cortex-to-trabecular bone ratio and where lesions are rapidly visible as endosteal notches, this technique is difficult to detect lesions within the trabecular network, vertebral in particular, of which 30–50% must be destroyed before osteolysis becomes noticeable[17]. The technique is also in difficulty for the interpretation of diffuse osteopenia, does not allow analysis of extraosseous plasmocytic localizations, nor the assessment of response to treatment[18].

2.2 Bone scan

Bone scintigraphy with technetium-99m-labeled biphosphonates, a marker of osteoblastic activity, proves to be completely inefficient in detecting MM-related bone damage, which we have seen to be clearly osteolytic in nature: Only reconstructive phenomena can be demonstrated by this technique, which grossly underestimates bone damage.

2.3 Computed tomography (CT)

Bone CT or X-ray CT allows a more precise study of the bone structure and the detection of lesions that escape SRW. The dose reductions made possible by recent developments in the technique (multi-fold detectors, iterative reconstructions, etc.) make the associated irradiation completely acceptable. In addition to a precise analysis of bone destruction, the technique allows the study of soft tissues and therefore of extraosseous localizations. Consequently, its use was once limited to the study of a spinal segment, for example to study the simple osteopenic (senile, postmenopausal) or tumoral osteolytic character of a vertebral compression, and has been extended to a wider coverage of the axial skeleton[19].

Myelomatous infiltration has several aspects on CT: Osteolytic lesions with well-delineated contours, relatively homogeneous in size; possibly microlacunar diffuse osteolysis; “pseudoangiomatous” appearance related to the preservation of vertical bone trabeculae around the plasma cell infiltration; expansive lytic lesions that may resemble a metastasis of kidney, breast, or thyroid cancer[20].

Low-dose CT of the axial skeleton has been shown to be significantly more effective than SRW in detecting bone involvement and has been proposed as “first-line” imaging in several guidelines[21-23]. The correlation with other imaging methods is sometimes surprising. Unequivocal osteolysis may be seen on CT in a patient with ambiguous or even normal findings on spinal cord MRI...Conversely, a “pure medullary” infiltration on MRI may be unrecognized by CT, which assesses the destruction of the trabecular network.

The performance of the technique for the assessment of lesion response is limited: very “subjective” perception of the normalization of the bone marrow signal, only possible measurement of the size reduction of extraosseous tumor masses as a true response criterion, whereas osteolysis often persists for a long time despite efficient treatment[24-26]. Also, the diagnostic value, prognostic interest, and ability to assess response to treatment that have been shown by whole-body MRI and PET/CT currently make these two techniques preferable to CT.

2.4 Positron emission tomography (PET-Scan)

18-fluorodeoxyglucose PET is imaging based on the tumor cell metabolism and depends on the affinity of these cells for the tracer used. FDG is the tracer used in MM as in most cancers. The value of PET in MM has not been fully validated. Its lesion detection capacity at the time of diagnosis is inferior to that of MRI, especially in diffuse forms and forms with few medullary foci. It is now routinely combined with CT, which brings its sensitivity to the detection of osteolysis. PET is promising for the evaluation of the therapeutic response. Its interest seems to be mainly prognostic[27]. The disappear-

ance of abnormalities after treatment suggests a better progression-free survival and overall survival. PET could also detect early those patients at high risk of recurrence after intensive treatment.

3. MRI and bone marrow involvement

3.1 From the axial skeleton to the whole body

MRI has, since its advent, demonstrated its ability to study the marrow content of bones, a compartment that had been largely unexplored by imaging methods. And then, studies on cadavers and then on living subjects firstly studied normal bone marrow, and in particular the appearance and distribution of its "red", hematopoietic components, confined in adults within the axial skeleton, and "yellow" occupying the peripheral skeleton[28]. Early work also investigated variations in bone marrow appearance with age and variants of normal. Early on, the ability of MRI to detect infiltration of normal bone marrow by oncologic affections-bone metastases from "osteophilic" solid cancers and M-was highlighted[29-34].

Work initially studied segments of the spine, for technical reasons, and for reasons of preferential tropism of MM and bone metastases. The location of skeletal damage by MM corresponds in fact to the topography of the red, hematopoietic marrow, where the abnormal plasma cells are located, and which has favorable local trophic factors and vascular permeability (sinusoids). MRI examinations were then extended to the entire spine and soon enriched with coverage of the bony pelvis in a so-called "axial skeleton MRI" approach, increasing the coverage of regions likely to be infiltrated by MM[35,36]. More recently, the study of the whole body in MRI has proved possible, thanks to technical advances affecting both the equipment (table mobility, surface antennas...), the sequences and the acquisition modalities (fast imaging, diffusion imaging...).

"Whole-body MRI," appeared in the late 1990s, has reached maturity, enriched with so-called "diffusion imaging" sequences, and is being promoted to the forefront of current diagnostic methods.

3.2 Acquisition technique

The T1-weighted spin-echo sequence is the basis for the investigation of the bone marrow in MRI. It rapidly and reproducibly investigates the signal of the bone marrow, which is primarily the reflection of its composition of fat and more hydrated cellular structures of physiological or pathological origin. Sensitive to a reduction in the proportion of fat in the bone marrow during tumor colonization, it is sufficient in most cases to detect focal or more diffuse medullary involvement, even before the activation of osteoclasts and osteoblasts and therefore before the appearance of osteolysis or osteocondensation detectable on radiography or CT (**Figure 1**). These T1-weighted sequences were very quickly supplemented by T2-type sequences, most often acquired with suppression of the fat signal or in STIR technique, increasing the sensitivity of the technique for the search for medullary infiltration[34].

Injection of contrast medium (gadolinium chelate) is rarely necessary, which was used just when there is ambiguity in interpretation of T1-weighted images obtained in spontaneous contrast. These injected sequences are then useful to distinguish normal hyperplastic marrow from incipient myelomatous infiltration. Normal bone marrow shows in effand in adults normally no perceptible enhancement on T1-weighted images performed after injection, whereas neoplastic infiltration results in marked enhancement that can be detected visually or by quantification of signal enhancement[37]. This contrast injection is sometimes used to assess the response of focal lesions[38].

The MRI study of the complete spine and pelvis covers about 90% of the "red" marrow capital. It is on this axial skeleton that the research work and the first wave of clinical use of MRI in MM have focused. The acquisition at the level of the spine is performed in the sagittal plane, at the level of the cervico-thoracic and lumbosacral segments, and classically includes T1-weighted sagittal and STIR slices. At pelvic level, the acquisition is performed in a coronal plane (T1 frontal slices) (**Figure 1**). The value of imaging the pelvis should be emphasized: It not only increases the proportion of hematologically active marrow investigated, but also al-

lows detection of lesions at risk of fracture, for example in the proximal femurs, or identification of lesions that may be targeted for biopsy in case of diagnostic ambiguity.

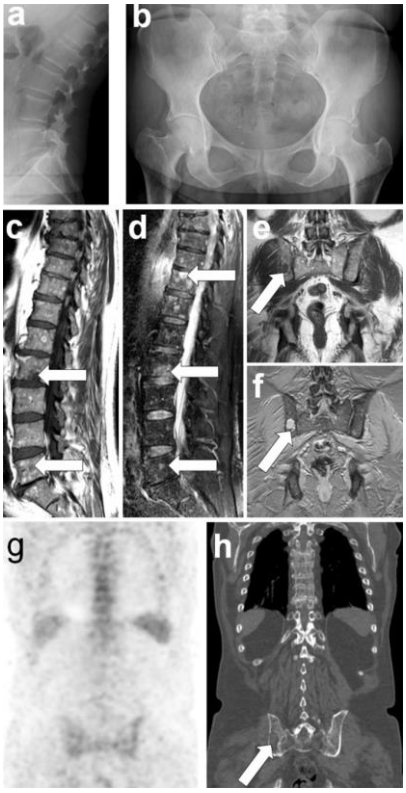

Figure 1. Multiple myeloma in a 57-year-old patient: stage 1A according to the Durie and Salmon classification, stage 2 according to the International Staging System: confrontation of imaging methods. The standard radiographic workup (**a** and **b** illustrating the lumbar spine and pelvis) is negative. Axial skeletal MRI (**c**-**f**) shows multiple foci of spinal cord replacement in the thoracolumbar spine (arrows in **c** and **d**) and pelvis (arrows in **e** and **f**), indicating by modern staging methods advanced disease (Durie and Salmon PLUS, IMWG). PET/CT with 18 fluorodeoxyglucose (**g**, **h**) does not show a hypermetabolic focus (**g**); the only positive finding is a right posterior iliac lytic focus (arrow in **h**).

Whole-body MRI is the consecutive acquisition of high-resolution images of limited body segments, which are then fused by a computer tool. It is the current preferred approach to study MM in MRI. It allows coverage of the entire skeleton, often limited to a study covering the body from head to mid-femur (rather than head to toe), which reduces the duration of the examination and sufficiently studies the territories involved in neoplastic spinal cord infiltration. A whole-body MRI examination typically combines so-called anatomical sequences, corresponding to the classic T1 and STIR weightings, already used in MRI assessments limited to the axial skeleton, and so-called diffusion-weighted imaging (DWI) sequences, which sensitize the examination to the detection of bone involvement, allow a quantitative approach to it, and appear cardinal for the evaluation of the therapeutic response.

These two types of sequences, based on quite different physical principles (medullary replacement for anatomical sequences, alteration of free water movements for diffusion sequences), complement each other: Diffusion imaging, because of the high contrast it offers between lesions and their environment, “draws the eye” to these lesions, in the manner of a nuclear medicine examination (scintigraphy or PET) and brings a “functional” or metabolic dimension to the imaging examination (**Figure 2**). It assesses the diffusion properties of water molecules and reflects the cellular richness and integrity of cell membranes. It studies their variations over time, especially during treatment. “Anatomical” imaging allows localization of lesions and recognition of the few false-positive findings (angiomas, osteoporotic settlement, degenerative pathology) from diffusion imaging[39].

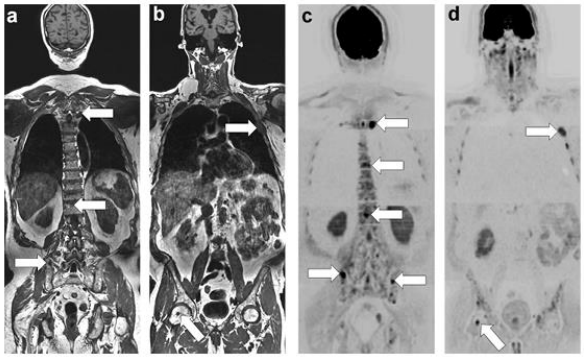

Figure 2. Newly diagnosed multiple myeloma in a 63-year-old patient: whole body MRI workup. Frontal T1 sections (**a**, **b**) and diffusion imaging (**c**, **d**): multiple foci of spinal cord replacement within the thoracolumbar spine and pelvis (arrows in **a** and c), costal gril, and right femoral head (arrows in **b** and **d**) signaling advanced disease requiring therapeutic management.

3.3 Semiology of myeloma damage on MRI

Bone marrow involvement in MM can present several aspects on MRI, observed both on axial skeletal and whole-body scans.

Bone marrow infiltration may be focal, characterized by the presence of foci of more or less depressed signal on T1 weighting, elevated on T2 weighting with suppression of fat and STIR signal, showing enhancement on T1 sequences performed after injection, and of intense signal on diffusion

imaging. More rarely, myelomatous lesions show a spontaneously intense T1 signal appearance that may make their detection difficult because of the spontaneously high signal of normal bone marrow due to its fat content. Spinal cord infiltration can be diffuse characterized by a diffuse lowering of the T1-weighted signal of the marrow (its signal then becomes lower than that of the intervertebral discs and paraspinal muscles), its elevation in T2 or STIR weighting, marked enhancement after gadolinium injection, and diffuse abnormalities on diffusion imaging. Diffuse and focal infiltration patterns may coexist. A "micronodular" or "salt-and-pepper" appearance is sometimes encountered, characterized by the existence of multiple distinctly sub-centimeter foci of abnormal spinal cord signal.

It should be noted that the bone marrow may retain a completely normal appearance in MM, in 50–75% of patients with an early form (stage 1 or indolent myeloma), but also in 20% of patients with advanced disease (stage 3), despite demonstration of abnormal plasmacytosis on bone biopsy. This aspect of preserved bone marrow signal most likely results from an insufficient alteration of the physiological balance between normal and tumor cells within the bone marrow in cases of limited "interstitial" plasma cell infiltration[40,41].

4. Roles and indications of MRI in MM

Regardless of staging systems, MRI is the technique of choice for the development of any spinal pain or neurologic symptoms in a patient with known MM. As part of a systematic approach to staging of the disease in an asymptomatic patient, it is increasingly becoming a first-line procedure, replacing SRW. It also has prognostic value.

4.1 Assessment of the symptomatic patient

In current clinical practice, MRI is the first-line imaging to be used in case of suspected spinal complications of MM such as vertebral compression, extraosseous epidural extension in particular, and radicular or spinal cord compression. The MRI examination should cover the entire spine, because of the diffuse nature of the disease and the possible coexistence of several localizations or complications[42]. It includes the classical T1, T2 weighted sequences, possibly supplemented by T1 weighted sequences performed after gadolinium injection.

MRI can more reliably distinguish the benign, simple osteoporotic, or on the contrary malignant, tumoral, character of a vertebral settlement than X-rays and CT[43,44]. In this respect, MM is a special case, compared to metastatic disease, where the settlements associated with the disease are typically tumoral. The application to MM of the criteria for distinguishing benign or malignant settlements thus shows that nearly two-thirds of the settlements observed in MM have a "benign" appearance and are related to the diffuse osteoporosis characteristic of the disease, and that only one-third of these settlements have a frankly malignant tumor appearance[16]. The frequently "benign" nature of the settlements-occurring at the level of a vertebra with a normal spinal cord signal-often makes it illusory to predict the level of occurrence of a settlement during iterative MRI evaluation of the spine[45].

4.2 Systematic detection of spinal cord injury: Staging and quantification

The role of MRI in a patient with suspected MM is to look for possible spinal cord lesions, the presence of which definates an advanced stage of the disease.

The quantification of focal lesions and determination of the type of spinal cord infiltration (focal, diffuse, mixed focal and diffuse) is important: The number of lesions (less than 5; between 5 and 20; greater than 20) forms the basis of Durie-Salmon PLUS staging (**Figure 1**). This quantitative approach is also important for prognostic assessment (see below).

A single lesion larger than 0.5 cm in diameter leads to a diagnosis of symptomatic MM according to the IMWG recommendations[9]. In case of doubt, a follow-up examination can be proposed.

Diffusion imaging allows a quantification of the "tumor burden" based on the proportion of skeletal tissue with marked alteration of a measurable parameter, the average diffusion coefficient (ADC), signaling neoplastic infiltration. The measurement of this parameter allows not only the detection of

medullary infiltration, but also its quantification and overall assessment of its response to treatment[46,47].

4.3 Clinical and biological prognosis

The incorporation of imaging into the initial staging of patients with newly diagnosed MM is based on the observation of the prognostive pejorative value of detecting bone involvement by these techniques. This is true both for standard radiographs in the historical staging of Durie and Salmon[7] and for MRI in newer staging systems[9].

In MM, MRI has repeatedly demonstrated its prognostic value in both early asymptomatic and advanced forms. In early forms (MGUS, indolent myeloma, stage 1) in which most patients have a bone marrow appearance on MRI, the finding of focal lesions or even diffuse infiltration reflects a high risk of rapid progression to advanced symptomatic MM requiring therapeutic management[4,35,48]. In advanced stages, the existence of a high number of focal lesions or diffuse infiltration of the bone marrow on MRI has a pejorative value in terms of survival[5,36,49]. The appearance of the bone marrow on MRI at the time of diagnosis correlates with the risk of occurrence of bone complications, especially vertebral compression: Patients with a high number of focal lesions or a picture of diffuse marrow infiltration are at significantly increased risk[50].

The prognostic value of MRI is very important in solitary plasmacytoma: This disease is characterized by the existence of a single plasma cell focus on radiographic workup, in the absence of signs of systemic disease (no serum monoclonal peak, less than 5% plasma cells on bone marrow biopsy...). MRI study of the axial skeleton or the whole body shows that nearly 80% of these patients have multifocal disease from the start and thus suggests the insufficient character of the only targeted and isolated therapeutic approach (radiotherapy) of the presumed single focus[51].

MRI seems to have a prognostic value in patients treated by bone marrow transplantation: The severity of abnormalities detected before treatment and especially the persistence of abnormalities after induction chemotherapy have a pejorative value in terms of therapeutic response and survival[52,53].

5. Comparison of MRI with other techniques

Since its advent, MRI has been compared to the "standard" SRW for the detection of myeloma involvement. Early studies showed that "for equal territory", MRI showed more lesions than radiographs, especially at the level of the spine and pelvis. Nevertheless, a MRI workup limited to this axial skeleton was not sufficient to replace BRS, particularly because of the diagnostic cost-effectiveness represented by radiographs of the skull and costal grid[54,55]. Multiple studies have subsequently shown the superiority of whole-body MRI over SRW[47,56,57]. Whole-body MRI has been compared with whole-body CT. MRI seems to win in terms of detection of spinal cord injury[58]. It is particularly useful for assessing the therapeutic response, which is much better than CT (persistence of osteolytic foci despite the spinal cord response).

Whole-body MRI represents, together with PET/CT, the technique of choice for current imaging of MM. Comparisons between these techniques are ongoing[59,60]. The former seems to prevail in terms of lesion detection, especially in cases of low-volume or, on the contrary, diffuse disease[61] (**Figure 1**). The latter seems to be of interest especially for the evaluation of the therapeutic response: "scarring" lesions could thus persist on MRI scans performed in the early therapeutic course, whereas PET/CT very quickly objectifies an extinction of the metabolic activity[62].

Conflict of interest

The authors declare that they have no conflict of interest.

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