Guideline paper

The Role of Magnetic Resonance Imaging in the Management of Patients with Multiple Myeloma: a Consensus Statement on behalf of the International Myeloma Working Group

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Abstract

Purpose: The aim of IMWG was to develop practical recommendations for the use of magnetic resonance imaging (MRI) in multiple myeloma (MM).

Methodology: An interdisciplinary panel of clinical experts on MM and myeloma bone disease developed recommendations for the value of MRI based on published data through March 2014.

Results/Recommendations: MRI has high sensitivity for the early detection of marrow infiltration by myeloma cells compared to otherl radiographic methods. Thus MRI detects bone involvement in myeloma patients much earlier than the myeloma-related bone destruction, with no radiation exposure. It is the gold standard for the imaging of axial skeleton and for distinguishing benign versus malignant osteoporotic vertebral fractures. MRI has the ability to detect spinal cord/nerve compression and the presence of soft tissue masses and it is recommended for the work up of solitary plasmacytoma. Regarding smoldering/asymptomatic myeloma, all patients should have a WB-MRI (or spine and pelvic MRI if WB-MRI is not available) and if they have >1 focal lesion of a diameter of >5 mm, they should be considered as having symptomatic disease that requires therapy. In the cases of equivocal small lesions then a second MRI should be performed after 3-6 months and if there is progression in MRI then the patient should be treated as a symptomatic myeloma patient. MRI at diagnosis of symptomatic patients and after treatment (mainly post-ASCT) provides prognostic information. However, MRI is not recommended for the standard work up of myeloma patients as it does not change the treatment choice to-date.

Key words: multiple myeloma, bone disease, MRI, smoldering myeloma, MGUS

Introduction

Bone disease, characterized by the presence of osteolytic lesions, bone fractures or osteoporosis, is a significant cause of morbidity and mortality in multiple myeloma (MM). Therefore, the guidelines of the International Myeloma Working Group (IMWG) suggest that the presence of, even asymptomatic, bone disease in conventional radiography is a criterion of symptomatic MM that requires treatment [1].

In 2009, the IMWG indicated that whole body X-ray (WBXR) remains the gold standard for the evaluation of MM-related bone disease [2]. However, the detection limit of WBXR is very low; to detect an osteolytic lesion by WBXR a proportion of at least 30%-50% of the trabecular bone has to be resorbed [3]. Moreover, WBXR is not a suitable technique for the diagnosis of osteoporosis related to myeloma. This underscores the need for more appropriate imaging techniques. In the previous recommendations, the IMWG supported the implementation of magnetic resonance imaging (MRI) if there are no osteolytic lesions in WBXR [2]. However, the IMWG did not suggest the use of MRI for the definition of symptomatic myeloma. Thus, to-date, a patient with focal lesions on MRI but with no lytic lesions on WBXR and with no other CRAB criteria is considered as having smoldering/asymptomatic myeloma (SMM) and follow-up with no treatment is recommended. In this manuscript, we summarise all available data regarding the use of MRI in the management of MM and give practical recommendations for everyday clinical practice.

Methodology

An interdisciplinary panel of experts on myeloma bone disease and MRI performance in myeloma patients developed the recommendations based on evidence of published clinical or observational studies, meta-analyses and systematic reviews through March 2014. Expert consensus was used to propose recommendations in the absence of sufficiently published data. The paper was drafted and circulated among all panel members followed by subsequent rounds of revisions till consensus achieved.

Magnetic Resonance Imaging Techniques for Myeloma

Several MRI techniques have been developed for the assessment of the bone marrow involvement in MM: T1-weighted, T2-weighted with fat suppression, short time inversion recovery (STIR) and gadolinium T1-weighted with fat suppression [4]. Myeloma lesions show typically a low signal intensity on T1-weighted images, a high signal intensity on T2-weighted and STIR images and often enhancement on gadolinium enhanced images [5,6].

Limitations of MRI are the prolonged acquisition time, the high cost, the exclusion of patients with metal devices in their body, the difficulties in cases of claustrophobic patients and the limited field of view. To override these restrictions, a WB-MRI methodology, which does not usually require contrast infusion, was developed. The time of WB-MRI is approximately 45 min. Although of interest, this newer technique is not yet widely employed.

All above MRI methods use MRI exquisite contrast and spatial resolution for the depiction of the WB anatomy and specific tissue composition in details. A newer MRI

sequence is the diffusion-weighted imaging (DWI). This functional technique demonstrates alterations in intra- and extracellular water content from disruption of the transmembrane water flux that are visible before identified changes on the morphologic routine sequences [7-9]. One disadvantage of DWI is that the apparent diffusion coefficient (ADC) is not exclusively influenced by diffusion but also by perfusion. However, improved sequences are under development to differentiate both influences [10]. DWI can be used to detect regions with bone marrow infiltration for both diagnosis and monitoring treatment response [11,12]. In MM patients the ADC was reproducible [13] and correlated with bone marrow cellularity and microvessel density (MVD) [14]. The dynamic contrast-enhanced MRI (DCE-MRI) is another MRI technique in which the distribution of a contrast agent inside and outside the blood vessels is assessed by computer-based analysis of repeated images over time. The analysis provides data for blood volume and vessel permeability for the assessment of microcirculation [15,16]. More importantly in MM patients, DCE-MRI measurements correlated with marrow angiogenesis and MVD [17] as well as in angiogenic response to therapy [18]. Positron emission tomography in combination with MRI (PET-MRI) is a novel and promising new methodology in which the PET part detects active focal lesions, while the MRI part shows the location of the lesions and gives information on myeloma cell infiltration of the bone marrow. Especially in patients who reach a complete remission (CR), this technique might be able to localize residual sites of disease activity and therefore may help to guide treatment in the future [19].

MRI Patterns of Marrow Involvement

Five MRI patterns of marrow involvement in myeloma have been recognised: (1) normal appearance of bone marrow; (2) focal involvement (positive focal lesion is considered the lesion of a diameter of at least 5mm); (3) homogeneous diffuse infiltration; (4) combined diffuse and focal infiltration; and (5) variegated or "salt-and-pepper" pattern with inhomogeneous bone marrow with interposition of fat islands [20,21]. Low tumor burden is usually associated with a normal MRI pattern, but a high tumor burden is usually suspected when there is diffuse hypointense change on T1-weighted images, diffuse hyperintensity on T2-weighted images and enhancement with gadolinium injection [22]. In several studies, the percentage of symptomatic patients with each of the abnormal MRI bone marrow patterns ranges from 18-50% for focal pattern, 25-43% for diffuse pattern and 1-5% for variegated pattern [16].

MRI in Symptomatic Myeloma

MRI versus Conventional Radiography and Other Imaging Techniques for the Detection of Bone Involvement: MRI is more sensitive compared to WBXR for the detection of bone involvement in MM. In the largest series of patients published to-date, MRI was compared to WBXR in 611 patients who received tandem autologous transplantation (ASCT). MRI and WBXR detected focal and osteolytic lesions in 74% and 56% of the imaged anatomic sites, respectively. Furthermore, 52% of 267 patients with normal WBXR had focal lesions on MRI. More precisely, MRI detected more focal lesions compared to lytic lesions in WBXR in the spine (78% *vs.* 16%; $p<0.001$), the pelvis (64% *vs.* 28%; $p<0.001$) and the sternum (24%*vs.* 3%; $p<0.001$). WBXR had

better performance than MRI in the ribs (10% *vs.* 43%; p<0.001) and the long bones (37% *vs.* 48%; p=0.006) and equal results in the skull and the shoulders [23]. Similar results had been previously reported in smaller studies, where MRI was superior to WBXR for the detection of focal vs. osteolytic lesions in the pelvis (75% *vs.* 46% of patients) and the spine (76% *vs.* 42%), especially in the lumbar spine [24-28]. In another small study (n=24) the DWI-MRI also showed a clear superiority when compared with X-rays in the exploration of the focal lesions in the cervical (56 vs. 0%, p<0.001), dorsal (81vs. 31%, p<0.0002) and lumbar spine (70 vs. 35%, p<0.0124), the pelvis (81 vs. 33%, p<0.0005) and the ribs (74 vs. 36%, p<0.0009) [28]. A recent meta-analysis confirmed the superiority of MRI over WBXR regarding the detection of focal lesions and showed that MRI especially outscores WBXR in the axial skeleton. However, WBXR detected more lesions than MRI in the ribs (43% vs. 10%), while there was no difference between MRI and WBXR in the number of lesions detected in the skull, clavicles and long bones [29].

Although it is clear that MRI can detect bone marrow focal lesions long before the development of osteolytic lesions in the WBXR, other imaging techniques such as PET combined with computed tomography (PET/CT), CT or WB-CT detect more osteolytic lesions compared to WBXR [29]. Do we have any evidence that MRI is superior to the other techniques in depicting bone involvement in myeloma? In a study with 41 newly-diagnosed MM, WB-MRI was found superior to WB-CT in detecting lesions in the skeleton [30]. In a prospective study, Zamagni et al compared MRI of the spine and pelvis with WBXR and PET-CT in 46 MM patients at diagnosis. Although PET-CT was superior to WBXR in detecting lytic lesions in 46% of patients (19% had negative

WBXR), it failed to reveal abnormal findings in 30% of patients who had abnormal MRI in the same areas, mainly of diffuse pattern. In that study, the combination of spine and pelvic MRI with PET-CT detected both medullary and extramedullary active myeloma sites in almost all patients (92%) [31]. Nevertheless, the Arkansas group was not able to confirm any superiority of MRI over PET/CT in the detection of more focal lesions in a large number of patients (n=303) within the total therapy 3 protocols [32]. Still, in 188 patients who had at least one focal lesion in MRI, MRI was superior to PET/CT regarding the detection of higher number of focal lesions (p=0.032). Furthermore, in this study the presence of diffuse marrow pattern was not taken into consideration as an abnormal MRI finding [32]. Compared to sestamibitechnetium-99m (MIBI) scan, WB-MRI detected more lesions in the vertebrae and the long bones, produced similar results in the skull and was inferior in the ribs [33]. The recent meta-analysis suggested that both MRI and PET-CT detected more bone involvement compared to WBXR, with up to 80% more lesions detected by the newer imaging techniques. However, MRI (1.12-1.82) outscored CT, PET and PET-CT (respectively 1.04-1.33; 1.00-1.58 and 1.27-1.45) regarding extra detection, but the ranges were large. Furthermore, regarding specificity, MRI outscored both PET and PET-CT when taking WBXR as the reference test [29]. One important question in this point is the value of WB-MRI, which is not available everywhere, over the MRI of the spine and pelvis. In 100 patients with MM and MGUS who underwent WB-MRI, 10% presented with focal lesions merely in the extra-axial skeleton. These lesions would have been ignored if only MRI of the spine and pelvis had been performed [34].

Other advantages of MRI over WBXR and CT include the discrimination of myeloma from normal marrow [4,35]; this finding can help in the differential diagnosis between myeloma and benign cause of a vertebral fracture. This is of extreme importance in cases of patients with a vertebral fracture and no other CRAB criteria and no lytic lesions. The MRI can also accurately illustrate the spinal cord and/or nerve root compression for surgical intervention or radiation therapy [2,4]. Furthermore, the presence of soft tissue extension of MM and the presence of extramedullary plasmacytomas that are developed in approximately 10-20% of patients during the course of their disease can be precisely visualized by WB-MRI [36-39]. MRI can also help in the better evaluation of avascular necrosis of the femoral head [39] and the presence of cardiac amyloidosis and/or soft tissue amyloid deposits [40]. Moreover, the tumor load can be assessed and monitored by MRI even in patients with non-secretory and oligosecretory MM [16].

Consensus Statement: MRI is the imaging gold standard method for the detection of bone marrow involvement in MM. MRI of the spine and pelvis can detect approximately 90% of focal lesions in MM and thus it can be used in cases where WB-MRI is not available. MRI is the procedure of choice to evaluate a painful lesion in myeloma patients, mainly in the axial skeleton. MRI is particularly useful in the evaluation of collapsed vertebrae, especially when myeloma is not active, where the possibility of osteoporotic fracture is high.

Prognostic Value of MRI: The prognostic significance of MRI findings in symptomatic myeloma has been evaluated. The largest study in the literature included 611 patients who received tandem ASCT-based protocols. Focal lesions detected by spinal MRI and not seen on WBXR independently correlated with overall survival (OS). In particular, cytogenetic abnormalities and >7 focal lesions on MRI distinguished three risk groups: 5-year OS was 76% in the absence of both criteria (n=276 patients), 61% in the presence of one of them (n=262), and 37% in the presence of both high-risk features (n=67). High number of MRI focal lesions (>7) correlated with high-risk disease features, such as high LDH and low albumin. Resolution of the focal lesions on MRI post treatment occurred in 60% of the patients who had superior survival. At disease progression after CR, MRI revealed new focal lesions in 26% of patients, enlargement of previous focal lesions in 28% and both features in 15% of patients [23]. In a more recent analysis of the same group on 429 patients, both WBXR-detected osteolytic lesions and MRI-detected focal lesions correlated with OS [41]. Patients with >2 osteolytic lesions in WBXR (n=133) had a 71% probability of OS at 3 years vs. 83% for those who had 1-2 lytic lesions (n=64; $p<0.0001$). Similarly patients who had >7 focal lesions in MRI (n=147) had a 73% probability of 3-year OS vs. 86% for those who had 0-7 focal lesions (n=235) and 81% for those who had diffuse pattern of marrow infiltration (n=47; p=0.04). PET/CT also produced similar results in the univariate analysis. In the multivariate analysis, from the imaging variables, only the presence of >2 osteolytic lesions in WBXR at diagnosis and the presence of >3 focal lesions in the PET/CT, 7 days post-ASCT had independent prognostic value for inferior OS (p=0.01 and 0.03, respectively). However, we have to mention the high percentage of patients

(232/429, 54%) who had no detectable osteolytic lesions by WBXR and the absence of evaluation of diffuse MRI pattern in this study [41].

The MRI pattern of marrow infiltration has also reported to have prognostic significance in newly diagnosed patients with symptomatic disease [22,42,43]. In the conventional chemotherapy (CC) era, Moulopoulos et al published that the median survival of newly diagnosed MM patients was 24 months if they had diffuse MRI pattern versus 51, 52 and 56 months for those with focal, variegated and normal patterns, respectively (p=0.001). In that study, the presence or absence of a diffuse MRI pattern separated patients with ISS stages I and II into two subgroups with significantly different survival times of 28 and 61 months, respectively (p=0.01). The presence of a diffuse MRI pattern predicted for inferior outcome independently of the presence of ASCT [22]. This is mainly because the diffuse MRI marrow pattern correlated with increased angiogenesis and advanced disease features [44,45]. The same group also reported the prognostic value of MRI patterns in 228 symptomatic MM patients who received upfront regimens based on novel agents. Patients with diffuse pattern had more often high-risk cytogenetics (50% vs. 31% in normal and focal patterns) and showed higher response rates with novel agent- over CC-based regimens (objective response: 88% vs. 46%, p<0.001). These patients, although they had inferior survival compared to patients with other MRI patterns, survived longer when they received novel agents upfront over CC (47 vs. 24 months; p<0.001). Moreover, the combination of diffuse MRI pattern, ISS-3 stage and high risk cytogenetics could identify a group of patients with very poor survival: median of 21 months and a probability of 3-year OS of only 35% [43]. Another study in 126 patients with newly diagnosed symptomatic myeloma who underwent an

ASCT showed that the diffuse and the variegated MRI patterns had an independent predictive value for disease progression (HR: 1.922; p=0.008) [45]. Finally, in patients with progressive or relapsed MM, an increased signal of DCE-MRI offered shorter PFS, possibly due to its association with higher MVD [15].

Consensus Statement: The number of MRI focal lesions (>7) and the presence of diffuse pattern correlate with inferior survival. Different treatment modalities are not justified for these patients to-date. Whether this prognostic effect of MRI represents a reflection of the tumor mass or whether the different growth patterns in the bone marrow represent discriminative biological entities has not been yet clarified.

MRI and Response to anti-Myeloma Therapy: An interesting finding is that a change in MRI pattern correlates with response to therapy. Moulopoulos et al firstly reported in the era of CC that CR is characterized by complete resolution of the preceding marrow abnormality, while partial response (PR) is characterized by changeover of diffuse pattern to variegated or focal patterns [46]. In a retrospective study that was conducted in the era of novel agents, response to treatment was compared with changes in infiltration patterns of WB-MRI before and after ASCT (n=100). There was a strong correlation between response to anti-myeloma therapies and changes in both diffuse (p=0.004) and focal (p=0.01) MRI patterns. Furthermore, the number of focal lesions at second MRI was of prognostic significance for OS (p=0.001) [47]. Another study in 33 patients who underwent an ASCT showed that WB-MRI data demonstrated progressive disease in 10 patients (30%) and response to high dose therapy in 23 (70%). Eight

(80%) of the ten patients with progressive disease revealed intramedullary lesions and two patients (20%) had intra- and extramedullary lesions. WB-MRI had a sensitivity of 64%, specificity of 86%, positive predictive value of 70%, negative predictive value of 83% and accuracy of 79 % for detection of remission [48]. This study supports that one of the disadvantages of MRI is that it often provides false positive results because of persistent non-viable lesions. Thus, PET/CT might be more suitable than MRI for determination of remission status [49]. Indeed in a large study of 191 patients, PET-CT revealed faster change of imaging findings than MRI in patients who responded to therapy [50]. It seems that the PET/CT normalization after treatment can offer more information compared to MRI for the better definition of CR [51].

To improve the results of MRI for the most accurate detection of remission, the DW-MRI has been recently used. In a first preliminary report, ADC values in active myeloma were significantly higher than marrow in remission [52]. Furthermore, the mean ADC increased in 95% of responding patients and decreased in all (n=5) non-responders (p=0.002). An increase of ADC by 3.3% was associated with response, having a sensitivity of 90% and specificity of 100%. Furthermore, there was a negative correlation between changes of ADC and changes of biochemical markers of response (r=-0.614; p=0.001) [53]. Further studies are definitely justified by these results.

Consensus Statement: MRI might help in the better definition of CR. Nevertheless, the high number of false positive results suggests that its combination with methods that reveal active lesions (i.e. PET-MRI) or another imaging method, such as PET-CT might be of more value in this setting. Thus the

systematic performance of MRI for the follow-up of the patients, in the absence of clinical indications, is not recommended.

The Value of MRI in the Definition of Smoldering/Asymptomatic Myeloma

The presence of lytic lesions by WBXR is included in the definition of symptomatic myeloma, based on studies showing that patients with at least one lytic lesion in WBXR have a median time to progression (TTP) of 10 months [54]. However, in patients with no osteolytic lesions in WBXR, the MRI reveals abnormal marrow appearance in 20-50% of them [21,22,55-57]; these patients are at higher risk for progression. Moulopoulos et al reported that patients with SMM and abnormal MRI studies required therapy after a median of 16months vs. 43 months for those with normal MRI ($p<0.01$) [55]. Hillengass and colleagues evaluated WB-MRI in 149 SMM patients. Focal lesions were detected in 42 (28%) patients, while >1 focal lesion was present in 23 patients (15%) who had high risk of progression (HR=4.05, $p<0.001$). The median TTP was 13 months and the progression rate at 2 years was 70%. On multivariate analysis, presence of >1 focal lesion remained a significant predictor of progression after adjusting for other risk factors including bone marrow plasmacytosis, serum and urine M protein levels and suppression of uninvolved immunoglobulins. In the same study, the diffuse marrow infiltration on MRI was also associated with increased risk for progression (HR=3.5, $p<0.001$) [56]. Kastritis and colleagues also showed in 98 SMM patients that abnormal marrow pattern in the MRI of the spine, which was present in 21% of patients, was associated with high risk of progression with a median TTP to symptomatic myeloma of 15 months ($p=0.001$) [57].

The identification of SMM patients who are at high risk for progression is of great importance because these patients may be benefited by immediate therapy. A recent randomized study from the Spanish Myeloma Study Group compared the combination of lenalidomide plus low dose dexamethasone (Rd) versus observation in patients with high-risk SMM (MRI was not used for defining high risk SMM). TTP was significantly longer with Rd compared to observation (median: not reached vs. 21 months, respectively, $p<0.001$). More importantly, Rd offered OS advantage (probability of 3-year survival 94% vs. 80%, respectively, $p=0.03$) [58].

An important issue is the management of patients who have 2 or more small focal lesions (<5mm) and if they have to be considered as patients with symptomatic myeloma. The Heidelberg group analyzed very recently the data of 63 SMM patients who had at least two WB-MRIs performed for follow-up before progression into symptomatic disease. The definition of radiological progression according to MRI findings included one of the following: i) development of a new focal lesion; ii) increase of the diameter of an existing focal lesion; and iii) detection of novel or progressive diffuse MRI pattern. The second MRI was performed 3-6 months after the performance of the first MRI. Evaluation of response according to IMWG criteria was also performed. Progressive disease according to MRI was observed in approximately 50% of patients, while 40% of patients developed symptomatic MM based on the CRAB criteria. In the multivariate analysis, MRI-PD was an independent prognostic factor for progression. Patients with stable MRI findings had no higher risk of progression, even when focal lesions were present at the initial MRI [59].

Consensus Statement: We recommend that patients with >1 unequivocal focal lesions (diameter of >5mm) should be considered as having symptomatic myeloma that requires therapy. Patients with equivocal focal lesions should repeat the MRI after 3-6 months and in cases of MRI progression the patient will be considered as a symptomatic patient who needs therapy. The biopsy of such lesions should be encouraged. Regarding diffuse MRI marrow pattern, we need further studies before its incorporation into the definition of symptomatic myeloma.

MRI findings in Monoclonal Gammopathy of Undetermined Significance (MGUS)

MGUS by definition is characterized by the absence of osteolytic lesions. However, MGUS patients have higher incidence of osteoporosis and vertebral fractures compared to normal population [60,61]. In a small study which included 37 patients with MGUS or SMM, MRI abnormalities were detected in 20% of them. These patients had a higher TTP to symptomatic myeloma compared to patients with a normal MRI who did not progress after a median follow-up of 30 months [62]. A prospective study in 331 patients with MGUS or SMM revealed that the detection of multiple (>1) focal lesions by MRI conferred an increased risk of progression [63]. In another large study, which included only MGUS patients (n=137) who underwent a WB-MRI at diagnosis, a focal infiltration pattern was detected in 23% of them. Independent prognostic factors for progression to symptomatic myeloma included the presence and number of focal lesions and the value of M-protein [64].

Consensus Statement: WB-MRI identifies MGUS patients with focal lesions that possibly represent accumulations of monoclonal plasma cells in the bone marrow. These patients seem to have increased risk of progression into myeloma and possibly MRI may be considered in the work-up of MGUS patients. Further confirmatory studies are needed.

MRI and Solitary Plasmacytoma of the Bone (SPB)

The diagnosis of SBP includes the presence of a solitary bone lesion, with a confirmed infiltration by plasma cells in the biopsy of the lesion; absence of clonal plasma cells in the trephine bone marrow biopsy and no CRAB criteria. Although definitive radiotherapy usually eradicates the local disease, the majority of patients will develop MM because of the growth of previously occult lesions which have not been detected by WBXR [65]. Moulopoulos et al published that spinal MRI revealed additional focal lesions in 4/12 SBP patients. After treatment with radiotherapy to the painful lesion, 3 patients developed systemic disease within 18 months from diagnosis [66]. Furthermore, Liebross et al observed that among SBP patients with spinal disease, 7/8 staged by WBXR alone developed MM compared to only 1/7 patients who also had spinal MRI [67].

Consensus Statement: MRI should be part of the staging procedures in patients with SBP, to better assess the extent of the local tumor and to reveal occult lesions elsewhere.

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References

1. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121:749-757, 2003
2. Dimopoulos M, Terpos E, Comenzo RL, et al: International myeloma working group consensus statement and guidelines regarding the current role of imaging techniques in the diagnosis and monitoring of multiple Myeloma. Leukemia 23:1545-1556, 2009
3. Durie BG, Salmon SE: A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 36:842-854, 1975
4. Moulopoulos LA, Dimopoulos MA: Magnetic resonance imaging of the bone marrow in hematologic malignancies. Blood 90:2127-2147, 1997
5. Libshitz HI, Malthouse SR, Cunningham D, et al: Multiple myeloma: appearance at MR imaging. Radiology 182:833-837, 1992
6. Weininger M, Lauterbach B, Knop S, et al: Whole-body MRI of multiple myeloma: Comparison of different MRI sequences in assessment of different growth patterns. Eur J Radiol 69:339-345, 2008
7. Attariwala R, Picker W: Whole body MRI: improved lesion detection and characterization with diffusion weighted techniques. J Magn Reson Imaging 38:253-268, 2013
8. Muller MF, Edelman RR: Echo planar imaging of the abdomen. Top Magn Reson Imaging 7:112-119, 1995

9. Wang Y: Description of parallel imaging in MRI using multiple coils. Magn Reson Med 44:495-499, 2000
10. Lemke A, Stieltjes B, Schad LR, et al: Toward an optimal distribution of b values for intravoxel incoherent motion imaging. Magn Reson Imaging 29:766-776, 2011
11. Xu X, Ma L, Zhang JS, et al: Feasibility of whole body diffusion weighted imaging in detecting bone metastasis on 3.0T MR scanner. Chin Med Sci J 23:151-157, 2008
12. Padhani AR, Koh DM: Diffusion MR imaging for monitoring of treatment response. Magn Reson Imaging Clin N Am 19:181-209, 2011
13. Messiou C, Collins DJ, Morgan VA, Desouza NM: Optimising diffusion weighted MRI for imaging metastatic and myeloma bone disease and assessing reproducibility. Eur Radiol 21:1713-1718, 2011
14. Hillengass J, Bäuerle T, Bartl R, et al: Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone marrow infiltration in patients with monoclonal plasma cell disease: a comparative study with histology. Br J Haematol 153:721-728, 2011
15. Hillengass J, Wasser K, Delorme S, et al: Lumbar bone marrow microcirculation measurements from dynamic contrast-enhanced magnetic resonance imaging is a predictor of event-free survival in progressive multiple myeloma. Clin Cancer Res 13:475-481, 2007
16. Hillengass J, Landgren O: Challenges and opportunities of novel imaging techniques in monoclonal plasma cell disorders: imaging "early myeloma". Leuk Lymphoma 54:1355-1363, 2013

17. Huang SY, Chen BB, Lu HY, et al: Correlation among DCE-MRI measurements of bone marrow angiogenesis, microvessel density, and extramedullary disease in patients with multiple myeloma. Am J Hematol 87:837-839, 2012
18. Zechmann CM, Traine L, Meissner T, et al: Parametric histogram analysis of dynamic contrast-enhanced MRI in multiple myeloma: a technique to evaluate angiogenic response to therapy? Acad Radiol 19:100-108, 2012
19. Fraioli F, Punwani S: Clinical and research applications of simultaneous positron emission tomography and MRI. Br J Radiol 87:20130464, 2014
20. Baur-Melnyk A, Buhmann S, Durr HR, Reiser M: Role of MRI for the diagnosis and prognosis of multiple myeloma. Eur J Radiol 55:56-63, 2005
21. Moulopoulos LA, Varma DG, Dimopoulos MA, et al: Multiple myeloma: spinal MR imaging in patients with untreated newly diagnosed disease. Radiology 185:833-840, 1992
22. Moulopoulos LA, Gika D, Anagnostopoulos A, et al: Prognostic significance of magnetic resonance imaging of bone marrow in previously untreated patients with multiple myeloma. Ann Oncol 16:1824-1828, 2005
23. Walker R, Barlogie B, Haessler J, et al: Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. J Clin Oncol 25:1121-1128, 2007
24. Ludwig H, Frühwald F, Tscholakoff D, et al: Magnetic resonance imaging of the spine in multiple myeloma. Lancet 2:364-366, 1987
25. Ghanem N, Lohrmann C, Engelhardt M, et al: Whole-body MRI in the detection of bone marrow infiltration in patients with plasma cell neoplasms in comparison to the radiological skeletal survey. Eur Radiol 16:1005-1014, 2006

26. Lecouvet FE, Malghem J, Michaux L, et al: Skeletal survey in advanced multiple myeloma: radiographic versus MR imaging survey. Br J Haematol 106:35-39, 1999
27. Tertti R, Alanen A, Remes K: The value of magnetic resonance imaging in screening myeloma lesions of the lumbar spine. Br J Haematol 91:658-660, 1995
28. Narquin S, Ingrand P, Azais I, et al: Comparison of whole-body diffusion MRI and conventional radiological assessment in the staging of myeloma. Diagn Interv Imaging 94:629-636, 2013
29. Regelink JC, Minnema MC, Terpos E, et al: Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. Br J Haematol 162:50-61, 2013
30. Baur-Melnyk A, Buhmann S, Becker C, et al: Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. AJR Am J Roentgenol 190:1097-1104, 2008
31. Zamagni E, Nanni C, Patriarca F, et al: A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica 92:50-55, 2007
32. Waheed S, Mitchell A, Usmani S, et al: Standard and novel imaging methods for multiple myeloma: correlates with prognostic laboratory variables including gene expression profiling data. Haematologica 98:71-78, 2013
33. Khalafallah AA, Snarski A, Heng R, et al: Assessment of whole body MRI and sestamibi technetium-99m bone marrow scan in prediction of multiple myeloma disease progression and outcome: a prospective comparative study. BMJ Open 3: pii: e002025, 2013

34. Bauerle T, Hillengass J, Fechtner K, et al: Multiple myeloma and monoclonal gammopathy of undetermined signifi cance: importance of whole-body versus spinal MR imaging. Radiology 252:477-485, 2009
35. Baur A, Stabler A, Bruning R, et al: Diffusion-weighted MR imaging of bone marrow: differentiation of benign versus pathologic compression fractures. Radiology 207:349-356, 1998
36. Moulopoulos LA, Dimopoulos MA, Weber D, et al: Magnetic resonance imaging in the staging of solitary plasmacytoma of bone. J Clin Oncol 11:1311-1315, 1993
37. Dimopoulos MA, Moulopoulos LA, Maniatis A, Alexanian R: Solitary plasmacytoma of bone and asymptomatic multiple myeloma. Blood 96:2037-2044, 2000
38. Varettoni M, Corso A, Pica G, et al: Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients . Ann Oncol 21:325-330, 2010
39. Lafforgue P, Dahan E, Chagnaud C, et al: Early-stage avascular necrosis of the femoral head: MR imaging for prognosis in 31 cases with at least 2 years of follow-up. Radiology 187:199-204, 1993
40. Syed IS, Glockner JF, Feng D, et al: Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging 3:155-164, 2010
41. Usmani SZ, Mitchell A, Waheed S, et al: Prognostic implications of serial 18-fluoro-deoxyglucose emission tomography in multiple myeloma treated with total therapy. Blood 121:1819-1823, 2013

42. Lecouvet FE, Vande Berg BC, Michaux L, et al : Stage III multiple myeloma: clinical and prognostic value of spinal bone marrow MR imaging. Radiology 209:653-660, 1998
43. Moulopoulos LA, Dimopoulos MA, Kastritis E, et al: Diffuse pattern of bone marrow involvement on magnetic resonance imaging is associated with high risk cytogenetics and poor outcome in newly diagnosed, symptomatic patients with multiple myeloma: a single center experience on 228 patients. Am J Hematol 87:861-864, 2012
44. Moulopoulos LA, Dimopoulos MA, Christoulas D, et al: Diffuse MRI marrow pattern correlates with increased angiogenesis, advanced disease features and poor prognosis in newly diagnosed myeloma treated with novel agents. Leukemia 24:1206-1212, 2010
45. Song MK, Chung JS, Lee JJ, et al: Magnetic resonance imaging pattern of bone marrow involvement as a new predictive parameter of disease progression in newly diagnosed patients with multiple myeloma eligible for autologous stem cell transplantation. Br J Haematol in press (doi: 10.1111/bjh.12820), 2014
46. Moulopoulos LA, Dimopoulos MA, Alexanian R, et al: Multiple myeloma: MR patterns of response to treatment. Radiology 193:441-446, 1994
47. Hillengass J, Ayyaz S, Kilk K, et al: Changes in magnetic resonance imaging before and after autologous stem cell transplantation correlate with response and survival in multiple myeloma. Haematologica 97:1757-1760, 2012

48. Bannas P, Hentschel HB, Bley TA, et al: Diagnostic performance of whole-body MRI for the detection of persistent or relapsing disease in multiple myeloma after stem cell transplantation. Eur Radiol 22:2007-2012, 2012
49. Derlin T, Peldschus K, Münster S, et al: Comparative diagnostic performance of ^{18} F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. Eur Radiol 23:570-578, 2013.
50. Spinnato P, Bazzocchi A, Brioli A, et al: Contrast enhanced MRI and ^{18} F-FDG PET-CT in the assessment of multiple myeloma: a comparison of results in different phases of the disease. Eur J Radiol 81:4013-4018, 2012
51. Bartel TB, Haessler J, Brown TL, et al: F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 114:2068-2076, 2009
52. Messiou C, Giles S, Collins DJ, et al: Assessing response of myeloma bone disease with diffusion-weighted MRI. Br J Radiol 85:e1198-1203, 2012.
53. Giles SL, Messiou C, Collins DJ, et al: Whole-Body Diffusion-weighted MR Imaging for Assessment of Treatment Response in Myeloma. Radiology 131529 (in press), 2014
54. Dimopoulos MA, Moulopoulos A, Smith T, et al: Risk of disease progression in asymptomatic multiple myeloma. Am J Med 94:57-61, 1993
55. Moulopoulos LA, Dimopoulos MA, Smith TL, et al: Prognostic significance of magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 13:251-256, 1995

56. Hillengass J, Fechtner K, Weber MA, et al: Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 28:1606-1610, 2010
57. Kastritis E, Terpos E, Moulopoulos L, et al: Extensive bone marrow infiltration and abnormal free light chain ratio identifies patients with asymptomatic myeloma at high risk for progression to symptomatic disease. Leukemia 27:947-953, 2013
58. Mateos M-V, Hernández M-T, Giraldo P, et al: Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 369:438-447, 2013
59. Merz M, Hielscher T, Wagner B, et al: Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia in press (doi: 10.1038/leu.2014.75), 2014
60. Pepe J, Petrucci MT, Nofroni I, et al: Lumbar bone mineral density as the major factor determining increased prevalence of vertebral fractures in monoclonal gammopathy of undetermined significance. Br J Haematol 134:485-490, 2006
61. van de Donk NW, Palumbo A, Johnsen HE, et al: The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica (in press), 2014
62. Vande Berg BC, Michaux L, Lecouvet FE, et al: Nonmyelomatous monoclonal gammopathy: correlation of bone marrow MR images with laboratory findings and spontaneous clinical outcome. Radiology 202:247-251, 1997

63. Dhodapkar MV, Sexton R, Waheed S, et al: Clinical, genomic, and imaging predictors of myeloma progression from asymptomatic monoclonal gammopathies (SWOG S0120). Blood 123:78-85, 2014
64. Hillengass J, Weber MA, Kilk K, et al: Prognostic significance of whole-body MRI in patients with monoclonal gammopathy of undetermined significance. Leukemia 28:174-178, 2014
65. Dimopoulos MA, Moulopoulos LA, Maniatis A, Alexanian R: Solitary plasmacytoma of bone and asymptomatic multiple myeloma. Blood 96:2037-2044, 2000
66. Moulopoulos LA, Dimopoulos MA, Weber D, et al: Magnetic resonance imaging in the staging of solitary plasmacytoma of bone. J Clin Oncol 11:1311-1315, 1993
67. Liebross RH, Ha CS, Cox JD, et al: Solitary bone plasmacytoma: outcome and prognostic factors following radiotherapy. Int J Radiat Oncol Biol Phys 41:1063-1067, 1998