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PHD THESIS

THE ROLE OF WHOLE-BODY MRI IN MULTIPLE MYELOMA DIAGNOSIS, STAGING, PROGNOSIS, AND TREATMENT RESPONSE ASSESSMENT

– A B S T R A C T –

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ABSTRACT

The chosen research topic is significant for two reasons: medical imaging has advanced significantly in the last decade, and newly emerging therapies in multiple myeloma have created a scientific gap in terms of assessing prognostic factors that may differ depending on the treatment.

Magnetic resonance imaging (MRI) is currently recommended by the NCCN guidelines as well as the International Myeloma Working Group (IMWG) guidelines as the first imaging method to be used in patients suspected of having MM, as well as in patients who have already been diagnosed and need to be assessed for total disease burden, treatment response, and cases with relapsing disease.Over the last decade, Whole-Body Magnetic Resonance Imaging (WB-MRI) has demonstrated extremely high sensitivity in evaluating and detecting bone marrow infiltration that is typical of multiple myeloma, changes that occur before the bone is destroyed. CT and x-rays, on the other hand, cannot detect marrow infiltration. The two techniques are only useful later in the disease when lytic lesions of the bone are present. Although MRI is a sensitive tool for depicting marrow infiltration patterns, extra-skeletal lesions, and tumour burden serologic criteria are currently used for staging of Multiple Myeloma, which can result in false positive or false negative results in some cases.

One of the driving forces behind my doctoral research was the fact that, to the best of my knowledge, the Hematology Department at Timisoara Municipal Hospital is the only place in Romania where patients with MM benefit from WB-MRI investigations. The phD thesis is composed of a general part where the current knowledge about multiple myeloma (clinical, paraclinical and treatment) is briefly reviewed (Chapter 1); in Chapter 2 I make a short review of the current imaging modalities used in MM and I present the current imaging guidelines dating from 2019; in the 3rd Chapter I make a thorough presentation of the WB-MRI technique used for MM patients. In the second part of the thesis, I will provide my own additions to the existing body of knowledge, which will be in the form of two observational studies; The first retrospective cohort study evaluates positive and negative prognostic imaging factors(WB-MRI) in multiple myeloma. The second retrospective study assesses treatment response using the WB-MRI technique and compares it to treatment response using serological criteria.

GENERAL PART

Multiple myeloma (MM) is a malignant disease that is included in a broad spectrum of hematological diseases of plasma cell interest that include monoclonal gammopathy of unknown significance (MGUS), smouldering myeloma, and plasma cell leukemia. One of the interesting specifications of MM is that antibody-forming cell clones (plasma cells) become malignant and thus

can cause unusual clinical manifestations with severe repercussions.MM was first described by Solly in 1844 and is characterised by a proliferation of a malignant plasma cell clone which then leads to a subsequent abundance of monoclonal paraproteins (M proteins)(1).

Most of the common signs and symptoms that are evident in MM can be explained by the abbreviation “CRAB”. The acronym CRAB stands for hypercalcemia, renal insufficiency, anemia, and lytic bone lesions that can be evidenced by imaging methods such as X-ray, computed tomography or MRI (2).

In the past, a diagnosis of MM required the presence of organ lesions as defined by the CRAB criteria (3). In 2015, the IMWG redefined the criteria for a diagnosis of MM by adding “myeloma-defining events”(3). Taking this into account, the CRAB criteria are now considered more or less obsolete, that is why treatment should be initiated before signs and symptoms included in the CRAB criteria occur. “Myeloma-defining events” as shown in Table 2 have been associated with near inevitable progression to end-organ damage and are thus defining biomarkers for MM. Taking this into consideration, high-risk patients can be diagnosed at an early stage if only one of the myeloma defining events is present(3). These biomarkers are important because being added to the diagnostic panel helps physicians start treatment earlier.

The revised IMWG criteria for active MM will increase the known prevalence of active MM and will change patients outcomes. The advised diagnostic workup in patients with some form of evidence of monoclonal protein should include routine blood counts, routine biochemistry that includes calcium, creatinine and albumin plasma levels. Beta 2 microglobulin should also be measured because this is a very important prognostic factor before treatment initiation. The patient should then undergo the three or four different techniques to measure monoclonal protein which include serum protein electrophoresis, urine protein electrophoresis with immunofixation and the serum free light chain test. All patients must undergo a bone marrow biopsy and the biopsy should include cytogenetics, “FISH” evaluation and immunohistochemistry(4, 5).

Because bone disease is a major complication of MM, imaging of the skeleton is important. The latest IMWG recommendations(6) dating from 2019 establish the use of different imaging methods. In suspected high-risk MGUS, the IMWG recommends whole-body CT to rule out multiple myeloma even if WB-MRI is a more sensitive method but less available in many hospitals. WB-MRI is recommended in patients with solitary bone plasmacytoma while PET-CT is recommended in plasmacytomas with extramedullary locations; complete yearly follow-up is recommended with the initial imaging method.In suspected MM the initial imaging method of choice are either whole body CT or FDG PET-CT; if whole-body CT is negative, and no other myeloma defining events are present, the use of whole-body MRI is recommended(6).

Currently, IMWG (International myeloma working group) recommends the use of modern imaging methods such as PET-CT, low-dose CT, whole-body MRI depending on the clinical indication and the resources of each hospital(6). As mentioned in the revised criteria(6), for the diagnosis of MM a single lytic lesion >5mm detected on CT or PET-CT is considered sufficient to meet the CRAB criteria regardless of whether this lesion is visible radiologically (a method with much lower sensitivity compared to modern methods).If abnormal FDG tracer uptake in the skeleton is visualised on PET-CT, underlying lytic lesions must be present for the changes to be classified as lesions in the context of multiple myeloma.However, osteodensitometry (DEXA) is not suitable for the diagnosis of MM as osteoporotic changes may also be associated with other physiological processes of the bones, such as ageing. Also, the presence of vertebral subsidence without evidence of associated osteolytic lesions is insufficient for the diagnosis of MM.

Whole-body MRI has been technically possible for several years and is finding more and more areas of application in medicine. This includes, in particular, applications in prevention and propagation diagnostics in neoplastic diseases. However, in individual fields the exact diagnostic value of the procedure must be evaluated. In addition, Whole-body imaging should not be applied uncritically, rather it must be weighed between the Whole-body MRI and dedicated and detailed examination of an organ or system. International guidelines now recommend WB-MRI in the management of patients with prostate cancer, melanoma and multiple myeloma(7).In the last two decades there have been multiple improvements in the scanning technique as well as in the hardware side of MRI systems which has led to improved magnetic field homogeneity and gradient systems which implicitly facilitated the introduction of new sequences such as DWI (8).

Multiple published papers highlighting the contribution of DWI in the detection, characterisation, and monitoring of response to treatment in all types of cancer, have made this sequence the mainstay of WB-MRI examination(9). With the improvement of the technique, examination times have dropped below 40min which has made the method common in many imaging laboratories, and the method has become a common one for the evaluation of many oncological pathologies (10, 11), including MM.

The WB-MRI examination can be customised according to the neoplastic pathology, thus in the case of patients diagnosed with MM the scanning protocol will evaluate the skeleton from the vertex up to the level of the knees; depending on the device used the images will be acquired at several stations, usually 5; the patient will be moved with the help of the examination table according to the scanning station in the iso-center of the magnet. The images are generally acquired in the axial plane, and it is generally desirable that the different sequences have the same number of slices for easier comparison. With modern software, images acquired in the axial plane (e.g., DWI) will be reconstructed to be examined as a whole-body; volumetric reconstructions can also be made for easier analysis of the tumor volume at the whole-body level (12).

Whole-Body MRI - Multiple Myeloma Protocols

Conventional MRI Sequences

The most common sequences for the evaluation of medullary infiltration are T1-weighted and T2-weighted; depending on their analysis, the amount of red and yellow marrow can be analysed, along with the possible tumour infiltration; in addition, there are chemical-shift sequences whose value is to differentiate bone with hematogenous marrow from tumour infiltrated bone. However, the T1 sequence is the most useful in the evaluation of bone marrow due to its increased fat content; thus, in cases of hematogenous marrow the signal will be increased compared to muscle(13).If increased contrast between different regions of the bone marrow is desired, fat-suppressive sequences such as FATSAT or STIR can be performed, the latter resulting in a more homogeneous saturation, being a less ‘pretentious’ sequence (14).

These conventional sequences will be used to assess the bone marrow and determine the type of tumour infiltration (15). They are also extremely useful sequences, being complementary to DWI in the assessment of treatment response, by normalisation of the signal intensity when the plasma cell infiltrate is replaced by hematogenous bone marrow with high fat content (15).

Diffusion Weighted Imaging (DWI)

DWI is an extremely good functional sequence in bone marrow analysis due to its sensitivity for assessing cell density as well as relative water and fat content (16). The DWI sequence is acquired in the axial plane using different b values (0, 50, 200, 600, 800 s/mm^2). The signal obtained will be directly proportional to the number of cells present per mm^2 as well as the strength of the diffusion gradient used (17).

The initial evaluation of the bone marrow will be done by examining the signal of the vertebral bodies in images with high b-values (generally b=800); thus, in case of evidence of lesions hyper-intense on DWI, they will be framed as areas of tumour infiltration if the ADC values are inversely proportional; this method of initial evaluation is extremely useful in practice as pathological lesions are extremely obvious to both the radiologist and the clinician(18).

MRI Imaging Patterns in Multiple Myeloma

Infiltrative and nodular lesions encountered in MM are T1 hypo-intense due to the quasi-absent fat content and increased amount of plasma cells; they generally show low T1 signal compared to muscle or intervertebral discs. On the other hand, lesions show hyper-intensity on T2 FAT SATURATION or STIR sequences due to high water and cell content, similar to other malignant bone lesions (19). MM lesions are present predominantly in the axial skeleton and

here we refer primarily to the vertebrae (66%), the bony pelvis (30%) and to a lesser extent the extra-axial skeleton (rib arches, limbs) (20).

Five types of bone marrow infiltration in multiple myeloma are described in the literature: normal appearing marrow, focal infiltration of the bone marrow, diffuse infiltration, ‘salt and pepper’ involvement, and combined focal and diffuse infiltration(21, 22).There are various studies appearing in the literature that correlate these types of medullary infiltration with the changes visualised in morpho-pathological examinations, thus validating them (23, 24). In the majority of cases of MM (28%), a normal appearance of the bone marrow is observed, with homogeneous T1 hyper-intensity; in the case of focal infiltration, various nodular focal T1 hypo-intense nodules are observed, which can occur anywhere in the skeleton; in the case of diffuse infiltration, diffuse T1 hypo-intense pattern is observed throughout the entire marrow, sometimes the signal being even lower than that of the intervertebral disc (in cases of severe medullary infiltration). In only 3% of cases a ‘salt and pepper’ pattern is seen and in 11% of cases a mixed diffuse and concomitant nodular infiltration pattern can be observed(22, 25).

SPECIAL PART

I. Whole-Body Diffusion-Weighted Magnetic Resonance Imaging and Apparent Diffusion Coefficient Values as Prognostic Factors in Multiple Myeloma

The role of imaging methods in multiple myeloma includes the whole panel of investigation in the case of an oncologic patient and ranges from diagnostic assessment of the extent and severity of bone and soft tissue lesions, identification, and quantification of complications to the periodic evaluation of the patient(26, 27).

Recent years have seen significant developments in imaging technology, with magnetic resonance imaging (MRI) becoming increasingly prevalent and Whole-Body MRI becoming increasingly important in the diagnosis and monitoring of multiple myeloma. While magnetic resonance imaging (MRI) is currently the gold standard for detecting bone marrow infiltration before macroscopic bone and marrow changes become apparent, there is compelling evidence to suggest that diffusion-weighted imaging could significantly improve both the detection rate and overall performance of MRI (DWI) (25, 27).

DWI, and by extension the apparent diffusion coefficient (ADC) values we acquire, provides a quantitative means of evaluating the extent of bone infiltration and a potential prognostic factor(27, 28).

The objective of this research was to determine whether or not the measurement of ADC values in newly diagnosed patients with multiple myeloma is a reliable indicator of how the disease will progress in the future and whether or not there is any correlation between ADC values and other independent prognostic factors, such as age, gender (male or female), stage I, II, or III multiple myeloma (according to the R-ISS classification), the type of marrow infiltration seen on conventional MRI sequences, or the treatment regimen used(27).

The investigation was carried out on a sample size of thirty-two patients who had been hospitalised at the Hematology Department of Timișoara Emergency Hospital between the dates of December 15, 2016, and December 31, 2019. The research was done in a retrospective manner, and patients who had recently been diagnosed with multiple myeloma (MM) as well as individuals who had at least one whole-body MRI both before and after induction therapy were considered for inclusion in the study. The inclusion criteria are presented in detail in the doctoral thesis.

Results and discussions

There were no correlations discovered between the baseline ADC and the age of the patient ($r=0.050$; $P=0.784$); similarly, there were no statistically significant differences detected between the baseline ADC and males and females(1.01 vs. 0.86; $P=0.520$).

According to the results of the Kruskall-Wallis test, there is a statistically significant difference in baseline ADC levels between the different groups of MRI marrow infiltration patterns ($p<0.001$). The results of a Paired Mann-Whitney U test that was performed with Bonferroni correction show that there is a statistically significant difference in baseline ADC levels between normal bone marrow and bone marrow with focal diffuse infiltration ($p=0.001$) and bone marrow with focal lesions ($p<0.001$), whereas there was no statistical difference between focal and diffuse infiltration vs focal lesions.

The Kruskall-Wallis test demonstrated that there is a statistically significant difference in baseline ADC values and disease stage($p=0.037$). Mann-Whitney U pairwise test conducted with Bonferroni correction show no statistically significant difference between stages II-III ($p=0.661$) while there is a significant difference between stages I-II ($p = 0.033$)(27).According to this, ADC values can differentiate between early disease (stage I) and more advanced disease (stages II and III). This is an interesting observation, as ADC values should be further used as a functional staging criteria to better assess and reveal occult lesions or discrete marrow infiltrations in newly diagnosed patients (27, 29).However, the existing guidelines for MM staging use only serum parameters, that is why the addition of imaging biomarkers such as ADC could help provide a more accurate staging method especially in cases with false-positive serological examples(27, 30).

Kruskall-Wallis test showed a statistical significant difference of initial ADC levels and treatment response types (p=0.045). Mann-Whitney U pairwise test conducted with Bonferroni correction show that responder patients (complete remission or partial remission) had lower initial ADC values compared to the non-responder group (stable disease of progressive disease)(27). However, larger studies are required to establish the exact cut-off value of ADC which can predict a good or poor outcome.

Based on the findings of the multivariate linear regression model, which we used to analyse our data, we found that the survival rate drops by 14.5 months for every point of ADC that is evident before therapy. Our regression equation turned out to be a decent fit for the model, explaining 57.8% of the total survival time adjusted R2=0.578)(27).

The survival of a patient after the pre-treatment ADC value can be roughly estimated using the following formula:

Survival (months) = 29.224 – (14.014 * baseline ADC value).

II. Whole-Body MRI Treatment Response Assessment: Imaging Response vs Serological Response

The aim of this study was to evaluate the sensitivity of the MDA morphological classification, the MDA-DWI morphological-functional classification in comparison with the serological criteria (“gold-standard”) in the assessment of treatment response as well as possible discrepancies that may appear. Another main objective of the study, was to evaluate the reproducibility of the method and possible discrepancies between experienced (consultant) and inexperienced (resident physician) radiologists.

Serological response (SERO) was considered the “gold-standard” for the assessment of treatment response; it was collected from the hospital’s CIS (clinical information system). Treatment responses following serological evaluation were categorised according to IMWG into SERO-CR (serological complete response), SERO-PR (serological partial response), SERO-SD (serological stable disease) and SERO-PD (serological progressive disease); these included only the assessment of treatment response according to laboratory tests, excluding imaging examinations.

In terms of imaging response, the group of patients was divided into 3 groups: normal marrow, focal nodular involvement, and focal and diffuse involvement. Two radiologists with different experience in MRI reviewed the images: a radiologist with more than 10 years’ experience in imaging (consultant radiologist) and a physician with less than 5 years’ experience (resident

physician). If there were discrepancies between the imaging opinions of the two physicians, a consensus was reached between the two by re-evaluation of the images by a third radiologist. Regarding the classification of lesions as target and non-target, nodular lesions were classified as target lesions while diffuse and 'salt and pepper' infiltration were considered as non-target lesions due to the impossibility of objective measurement.

In the study, we used two imaging criteria, namely the MD Anderson criteria (MDA) and the MDA-DWI criteria, the latter being a proprietary criterion adapted from the MDA but including the assessment of lesions in terms of DWI sequence and thus ADC values. The MDA criteria is an imaging model for the assessment of bone lesions and was developed by the MD Anderson Cancer Centre at the University of Texas in 2004 (31). It assumes the existence of 4 types of response to treatment: CR, PR, SD and PD.

The second imaging criterion for evaluating patients (MDA-DWI) consisted of adapting the MDA criterion with the incorporation of ADC measurements.

Both in the case of MDA and MDA-DWI criteria the measurements of the two radiologists were performed on 5 target lesions larger than 1 cm; if the patient presented less than 5 target lesions all lesions were measured; in the case of ADC measurements the same 5 lesions were evaluated and the values obtained for all lesions were averaged; if one of the lesions showed discrepant changes it was excluded from the evaluation. Both the imaging criteria and the concrete way of evaluating the lesions are presented in detail in the doctoral thesis.

Results and Discussions

There was a moderate agreement between serological response and MDA criteria ($\kappa = 0.42$) and an almost perfect agreement between the serological and the MDA-DWI criteria ($\kappa = 0.89$). This is the first study in which WB-MRI treatment responses are similar with the clinical criteria; several previous studies as well as the IMWG consensus stated that WB-MRI could show persistent non-viable lesions after treatment (32, 33); this is the consequence of using only the morphological sequences of WB-MRI in previous studies; after a lytic lesion is formed in the bone, even if the treatment is effective, the natural pathways of healing are usually represented by cystic degeneration and the formation of fluid filled cysts, that is why on conventional imaging examinations the lesions will be present indefinitely although in fact they show no mitotic activity. Another possible healing mechanism can be represented by sclerosis formation and size reduction of the lesions; in several studies published(34-36)sclerosis was observed at different time points after treatment initiation and ranged from 13% to 68% of all target lesions; however complete morphologic 'restitutio ad integrum' of the lytic lesions was not obtained in these studies; if a morphologic

imaging criteria would have been used in these patients, the imaging report would state a partial response; if the modified MDA-DWI criteria is used on these patients, complete response would be obtained after measuring the ADC values of the target lesions.

Compared to other previous studies(37, 38), when using both the morphological and the functional criteria (MDA-DWI) we obtained excellent sensitivity for PR (Se=100%) and CR (Se=86%); when using just the MDA criteria, WB-MRI had an extremely low performance with sensitivities of 52% for PR and 20% for CR. This can be explained by the fact that most myeloma lesions remain the same size after treatment although the internal signal, contrast uptake and ADC values suffer alterations; most of the lesions in the current study suffered a cystic transformation in responder patients, presenting as a 'shine-through' artefact when analysing both DWI and ADC maps.

Prior to this, there was only one other similar study that evaluated the imaging response compared to the serologic response using ADC as a parameter (38). However, in that study the sensitivity of WB-MRI using DWI was extremely low for predicting CR (only 4.5%) which can be of course explained by the fact that it was a small study, and the lesion measurement was different compared to the present research; moreover when I elaborated the present imaging score (MDA-DWI), I made a thorough research of the literature to see what percent of ADC value decrease is necessary to consider a lesion is in remission. In the studies found(39, 40), a statistically significant positive therapy response was observed when mean ADC values raised by more than 50%.

The MDA-DWI criteria also showed excellent correlations with non-responder patients; The Se for the SD and PD groups were 84.6% and 94.1% making this an extremely accurate imaging method; by comparison, the MDA criteria only had a Se of 61.5%(SD) and 52.9%(PD) when evaluating non-responders.

When evaluating the inter-reader agreement of the MDA-DWI criteria, there is an excellent correlation between consultant radiologist r=0.923 (0.874-0.952) and resident doctor =0.898 (0.835-0.937). This is similar to other studies that evaluate the inter-observer agreement of WB-MRI both in MM patients as well as in other malignancies (41-44).

When evaluating the inter-reader agreement of the MDA criteria, there was an agreement of 47% and a kappa value of 0.29 which means fair agreement. The consultant had an agreement of 39% and a kappa score of 0.27 which indicates fair agreement. The resident had an agreement of 29% and a kappa score of 0.18 which signifies minor agreement. This strongly demonstrates the important added value of the DWI sequence when evaluating treatment response in these patients.

Original Contributions

- There were no correlations between the initial ADC and patient age ($p>0.10$); no statistically significant differences were found between initial ADC and patient gender ($p>0.10$)
- The baseline ADC values were found to be much higher in patients with diffuse marrow infiltration and focal marrow lesions compared to those with normal appearing marrow.
- There was a statistical significant difference of initial ADC levels and treatment response types. Patients with complete remission or partial remission had lower initial ADC values compared to patients with stable disease or progressive disease.
- Kaplan-Meier survival analysis was conducted to compare the three groups of marrow infiltration. Survival estimates ranged from 25.2 months for patients with normal bone marrow to 12.7 months for those with focal and diffuse infiltration; this is an important finding which suggests that treatment options can be tailored according to the type of marrow infiltration pattern.
- When applying the multivariate linear regression model, I observed that for every point of ADC (pre-treatment values) the survival is decreased/reduced by 14.5 months. The regression equation proved to be a good fit for the model, explaining 57.8% of survival duration (adjusted $R2=0.578$).
- The survival of a patient after the pre-treatment ADC value can be estimated using the following formula:

  Survival (months) = 29.224 – (14.014 * baseline ADC value)

- Compared to other previous studies, when using both the morphological and the functional criteria (MDA-DWI) I obtained excellent sensitivity for PR ($Se=100\%$) and CR ($Se=86\%$); when using just the MDA criteria, WB-MRI had an extremely low performance with sensitivities of 52% for predicting PR and 20% for CR; the availability of DWI along with the morphologic sequences makes WB-MRI both an imaging technique as well as a functional criteria in evaluating treatment response.
- The MDA-DWI criteria also showed excellent correlations with non-responder patients; The Se for the SD and PD groups were 84.6% and 94.1% making this an extremely accurate imaging method; by comparison, the MDA criteria only had a Se of 61.5%(SD) and 52.9%(PD) when evaluating non-responders.
- When evaluating the inter-reader agreement of the MDA-DWI criteria, there is an excellent agreement between consultant radiologist $r=0.923$(0.874-0.952) and resident doctor $=0.898$ (0.835-0.937), making the method extremely reproducible.

Bibliography

1. Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111(6):2962-72.
2. Fonseca R, Jain T. Bone Disease in Myeloma: The Claws of CRAB. Clin Cancer Res. 2016;22(6):1301-3.
3. Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol. 2015;33(6):657-64.
4. Schjesvold F. Evolution of diagnostic workup and treatment for multiple myeloma 2013-2019. Eur J Haematol. 2020;105(4):434-48.
5. Juneja R, Pati H, Gupta G, Mahapatra M, Tyagi S, Saxena R. Diagnostic workup of multiple myeloma in resource-constrained setting: is addition of costly test to baseline profile necessary? The Egyptian Journal of Haematology. 2021;46(3):181-4.
6. Hillengass J, Usmani S, Rajkumar SV, Durie BGM, Mateos MV, Lonial S, et al. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol. 2019;20(6):e302-e12.
7. Summers P, Saia G, Colombo A, Pricolo P, Zugni F, Alessi S, et al. Whole-body magnetic resonance imaging: technique, guidelines and key applications. Ecancermedicalscience. 2021;15:1164.
8. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology. 1986;161(2):401-7.
9. Padhani AR, Liu G, Koh DM, Chenevert TL, Thoeny HC, Takahara T, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia. 2009;11(2):102-25.
10. Katscher U, Börnert P, Leussler C, van den Brink JS. Transmit SENSE. Magn Reson Med. 2003;49(1):144-50.
11. Padhani AR, Lecouvet FE, Tunariu N, Koh DM, De Keyzer F, Collins DJ, et al. METastasis Reporting and Data System for Prostate Cancer: Practical Guidelines for Acquisition, Interpretation, and Reporting of Whole-body Magnetic Resonance Imaging-based Evaluations of Multiorgan Involvement in Advanced Prostate Cancer. Eur Urol. 2017;71(1):81-92.
12. Winfield JM, Blackledge MD, Tunariu N, Koh DM, Messiou C. Whole-body MRI: a practical guide for imaging patients with malignant bone disease. Clin Radiol. 2021;76(10):715-27.
13. Silva JR, Jr., Hayashi D, Yonenaga T, Fukuda K, Genant HK, Lin C, et al. MRI of bone marrow abnormalities in hematological malignancies. Diagn Interv Radiol. 2013;19(5):393-9.
14. Shah LM, Hanrahan CJ. MRI of spinal bone marrow: part I, techniques and normal age-related appearances. AJR Am J Roentgenol. 2011;197(6):1298-308.
15. Sun M, Cheng J, Ren C, Zhang Y, Li Y, Wang L, et al. Evaluation of Diffuse Bone Marrow Infiltration Pattern in Monoclonal Plasma Cell Diseases by Quantitative Whole-body Magnetic Resonance Imaging. Acad Radiol. 2022;29(4):490-500.
16. Padhani AR, van Ree K, Collins DJ, D'Sa S, Makris A. Assessing the relation between bone marrow signal intensity and apparent diffusion coefficient in diffusion-weighted MRI. AJR Am J Roentgenol. 2013;200(1):163-70.
17. Khoo MM, Tyler PA, Saifuddin A, Padhani AR. Diffusion-weighted imaging (DWI) in musculoskeletal MRI: a critical review. Skeletal Radiol. 2011;40(6):665-81.

18. Padhani AR, Koh DM, Collins DJ. Whole-body diffusion-weighted MR imaging in cancer: current status and research directions. Radiology. 2011;261(3):700-18.
19. Dutoit JC, Vanderkerken MA, Anthonissen J, Dochy F, Verstraete KL. The diagnostic value of SE MRI and DWI of the spine in patients with monoclonal gammopathy of undetermined significance, smouldering myeloma and multiple myeloma. Eur Radiol. 2014;24(11):2754-65.
20. Collins CD. Multiple myeloma. Cancer Imaging. 2004;4 Spec No A(Spec No A):S47-53.
21. Baur-Melnyk A, Buhmann S, Dürr HR, Reiser M. Role of MRI for the diagnosis and prognosis of multiple myeloma. Eur J Radiol. 2005;55(1):56-63.
22. Costachescu D, Ionita H. The importance of bone marrow infiltration patterns in multiple myeloma seen on magnetic resonance imaging—Case report and imaging perspective. Clinical Case Reports. 2022;10(10):e6452.
23. Stäbler A, Baur A, Bartl R, Munker R, Lamerz R, Reiser MF. Contrast enhancement and quantitative signal analysis in MR imaging of multiple myeloma: assessment of focal and diffuse growth patterns in marrow correlated with biopsies and survival rates. AJR Am J Roentgenol. 1996;167(4):1029-36.
24. Ji X, Huang W, Dong H, Shen Z, Zheng M, Zou D, et al. Evaluation of bone marrow infiltration in multiple myeloma using whole-body diffusion-weighted imaging and T1-weighted water-fat separation Dixon. Quant Imaging Med Surg. 2021;11(2):641-51.
25. Dutoit JC, Verstraete KL. MRI in multiple myeloma: a pictorial review of diagnostic and post-treatment findings. Insights Imaging. 2016;7(4):553-69.
26. Mena E, Choyke P, Tan E, Landgren O, Kurdziel K. Molecular imaging in myeloma precursor disease. Semin Hematol. 2011;48(1):22-31.
27. Costachescu D, Ionita I, Borsi EC, Potre O, Potre C, Navolan DB, et al. Whole-body diffusion-weighted magnetic resonance imaging and apparent diffusion coefficient values as prognostic factors in multiple myeloma. Exp Ther Med. 2021;22(2):827.
28. Kwee TC, Takahara T, Ochiai R, Katahira K, Van Cauteren M, Imai Y, et al. Whole-body diffusion-weighted magnetic resonance imaging. Eur J Radiol. 2009;70(3):409-17.
29. Cavo M, Terpos E, Nanni C, Moreau P, Lentzsch S, Zweegman S, et al. Role of (18)F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. Lancet Oncol. 2017;18(4):e206-e17.
30. Li L, Dong M, Wang XG. The Implication and Significance of Beta 2 Microglobulin: A Conservative Multifunctional Regulator. Chin Med J (Engl). 2016;129(4):448-55.
31. Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT. Bone imaging in metastatic breast cancer. J Clin Oncol. 2004;22(14):2942-53.
32. Bannas P, Hentschel HB, Bley TA, Treszl A, Eulenburg C, Derlin T, 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. 2012;22(9):2007-12.
33. Dutoit JC, Claus E, Offner F, Noens L, Delanghe J, Verstraete KL. Combined evaluation of conventional MRI, dynamic contrast-enhanced MRI and diffusion weighted imaging for response evaluation of patients with multiple myeloma. Eur J Radiol. 2016;85(2):373-82.
34. Schulze M, Weisel K, Grandjean C, Oehrlein K, Zago M, Spira D, et al. Increasing bone sclerosis during bortezomib therapy in multiple myeloma patients: results of a reduced-dose whole-body MDCT study. AJR Am J Roentgenol. 2014;202(1):170-9.

35. Hinge M, Andersen KT, Lund T, Jørgensen HB, Holdgaard PC, Ormstrup TE, et al. Bone healing in multiple myeloma: a prospective evaluation of the impact of first-line anti-myeloma treatment. Haematologica. 2016;101(10):e419-e22.
36. Moulopoulos LA, Koutoulidis V, Hillengass J, Zamagni E, Aquerreta JD, Roche CL, et al. Recommendations for acquisition, interpretation and reporting of whole body low dose CT in patients with multiple myeloma and other plasma cell disorders: a report of the IMWG Bone Working Group. Blood Cancer J. 2018;8(10):95.
37. Hillengass J, Bäuerle T, Bartl R, Andrulis M, McClanahan F, Laun FB, 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. 2011;153(6):721-8.
38. Park HY, Kim KW, Yoon MA, Lee MH, Chae EJ, Lee JH, et al. Role of whole-body MRI for treatment response assessment in multiple myeloma: comparison between clinical response and imaging response. Cancer Imaging. 2020;20(1):14.
39. Lacognata C, Crimì F, Guolo A, Varin C, De March E, Vio S, et al. Diffusion-weighted whole-body MRI for evaluation of early response in multiple myeloma. Clinical Radiology. 2017;72(10):850-7.
40. Yamada A, Araki Y, Tanaka Y, Otsuki S, Yamada A, Moriyama M, et al. Relevance of diffusion-weighted imaging with background body signal suppression for staging, prognosis, morphology, treatment response, and apparent diffusion coefficient in plasma-cell neoplasms: A single-center, retrospective study. PLOS ONE. 2021;16(7):e0253025.
41. Messiou C, Kaiser M. Whole body diffusion weighted MRI--a new view of myeloma. Br J Haematol. 2015;171(1):29-37.
42. Croft J, Riddell A, Koh DM, Downey K, Blackledge M, Usher M, et al. Inter-observer agreement of baseline whole body MRI in multiple myeloma. Cancer Imaging. 2020;20(1):48.
43. Lai AYT, Riddell A, Barwick T, Boyd K, Rockall A, Kaiser M, et al. Interobserver agreement of whole-body magnetic resonance imaging is superior to whole-body computed tomography for assessing disease burden in patients with multiple myeloma. Eur Radiol. 2020;30(1):320-7.
44. Poulsen AEF, Axelsen MB, Poggenborg RP, Eshed I, Krabbe S, Glinatsi D, et al. Whole-body Magnetic Resonance Imaging in Psoriatic Arthritis, Rheumatoid Arthritis, and Healthy Controls: Interscan, Intrareader, and Interreader Agreement and Distribution of Lesions. J Rheumatol. 2021;48(2):198-206.