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Advanced Mri Techniques for Multiple Myeloma Detection and Management- Current Knowledge and Future Prospects

Mini Review

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Abstract

Multiple myeloma is a neoplastic disorder of plasma cells, characterized by bone marrow infiltration, with a high morbidity and mortality. Imaging plays an important role in diagnosis, prognosis and evaluation of treatment response. Whole-body CT remains the mainstay for screening, but MRI has emerged as the most sensitive technique for lesion detection. In this article we will review the new emerging imaging modalities and future developments concerning multiple myeloma.

Keyword: MRI, Multiple myeloma, musculoskeletal, Dixon, whole-body MRI, diffusion-weighted imaging, artificial intelligence

Abbreviations

^{1}H-MRS: Proton Magnetic Resonance; ^{18}F-FDG PET: 2-Deoxy-2-[Fluorine-18]-Fluoro-D-Glucose Positron Emission Tomography; ADC: Apparent Diffusion Coefficient; CT: Computed Tomography; DCE: Dynamic Contrast Enhanced; DWI: Diffusion-Weighted Imaging; EHA: Europaen Hematology Association; ESMO: European Society of Medical Oncology; IMWG: International Myeloma Working Group; IP: In-Phase; MM: Multiple Myeloma; MRI: Magnetic Resonance Imaging; MYRADS: Myeloma Response Assessment and Diagnosis System; OP: Out-of-Phase; SMM: Smoldering Multiple Myeloma; T1WI: T1-Weighted Imaging; T2WI: T2-Weighted Imaging; WBCT: Whole-Body Computed Tomography; WBMRI: Whole-Body Magnetic Resonance Imaging

Introduction

Multiple myeloma (MM) is the most common primary malignant neoplasm of bone in adults and the second most common hematological malignancy, accounting for 1-1,8% of all cancer [1]. MM is part of a spectrum of monoclonal gammopathies where there is monoclonal proliferation of plasma cells in hematopoietic locations (e.g. bone marrow), and is diagnosed with clinical, biological and radiological criteria. Bone marrow infiltration can have several different patterns, such as focal lytic lesions or focal lytic involvement, homogeneous diffuse infiltration, combined diffuse and focal involvement and a rarer osteosclerotic form [2]. Thus, a complete spatial survey of the appendicular and axial skeleton is needed to avoid misdiagnosis and adequately evaluate disease burden.

Detection of lytic bone lesions was traditionally performed with

conventional radiography [3]. More recently, the International Myeloma Working Group (IMWG) disease criteria published in 2014 recommended computed tomography (CT) or 2-deoxy-2-[fluorine-18]-fluoro-D-glucose positron emission tomography / computed tomography (^{18}F-FDG PET/CT) to detect smaller lesions. Superiority of whole-body CT (WBCT) over conventional radiography in detection of damage to mineralized bone has been acknowledged [4-6] and the technique has been incorporated as a first-line imaging modality by international consensus groups and associations. Currently, WBCT is obligatory for diagnosis and relapse evaluation according to European Hematology Association / European Society of Medical Oncology (EHA-ESMO) clinical practice guidelines [7], the ESMO guidelines [8] and IMWG consensus recommendations [9].

Recently, magnetic resonance imaging (MRI), an imaging modality that uses non-ionizing radiation to produce diagnostic images, has emerged as a promising technique with superior soft-tissue contrast compared to CT and functional capabilities matching molecular imaging. In fact, MRI is now considered the gold standard imaging technique for detection of bone marrow lesions [10]. This mini review addresses the advanced anatomical and functional techniques being developed for MRI in MM diagnosis and management.

Conventional Imaging Techniques

Whole-Body MRI

Whole-body MRI (WBMRI) is indicated in patients with negative or inconclusive imaging workup after WBCT and ^{18}F-FDG PET/CT is not carried out, with the intention of differentiating asymptomatic/smoldering and symptomatic MM [11]. MM lesions have high water and cellular content, appearing as hypointense on T1-weighted imaging (T1WI) and hyperintense on T2-weighted imaging (T2WI). Bone marrow infiltration has been described as diffuse bone marrow uptake superior to liver uptake [12,13]. Conventional MRI sequences are capable of detecting focal lesions before bone demineralization or destruction [14]. Detection of more than one focal lesion of at least 5 mm is sufficient to diagnose MM and, according to IMWG, these patients should be considered to have symptomatic disease that requires therapy [10].

MRI also has the ability to differentiate non-pathological from pathological fractures, which increases its specificity compared to PET imaging, and has superior soft-tissue contrast resolution making it ideal for detection of extramedullary MM [2,15]. Comparison of WBCT with WBMRI has shown that MRI revealed more widespread disease in 50% of patients [16,17]. As such, MRI is more sensitive and specific than other imaging methods such as conventional radiography, CT and PET, providing greater diagnostic accuracy without radiation exposure.

This technique, however, has some disadvantages: it has limited availability, higher costs, less impact on clinical decision [18] and WB-MRI may have a long acquisition time (45 minutes to 1 hour), making it less prone to patient compliance and technical success. In order to promote standardization of WBMRI acquisition, interpretation and reporting, a Myeloma Response Assessment and Diagnosis System (MY-RADS) has been developed by an expert panel of radiologists, medical physicists and hematologists [19].

Dixon Method

The Dixon method is an MRI sequence designed to separate water and fat signal and reconstruct pure water and pure fat images. Paired in-phase (IP) and out-of-phase (OP) images are acquired whereupon tissue signal alternates depending on the water/fat content ratio of voxels [20]. It is a reliable technique for fat suppression in areas subject to magnetic field inhomogeneities (e.g. extremities, neck). It is usually added as a complementary method to conventional MRI sequences.

During bone marrow maturation, cellular red marrow is replaced with fatty yellow marrow, in a centripetal fashion, until adulthood [20]. Areas of bone marrow reconversion from yellow to red marrow may occur in certain circumstances, most commonly when there is increased hematopoietic demand. The chemical composition of yellow marrow is mostly fat, while red marrow has roughly equal amounts of fat and water [21]. In contrast, local invasion by tumor cells leads to a cellular environment that disrupts water/fat ratio. With Dixon imaging, it is possible to separate the water and fat content of tissues and detect the presence or absence of fat in bone marrow signal changes detected using other sequences, such as reconverted marrow which may mimic neoplastic lesions. Loss of more than 20% signal on OP compared to IP images demonstrates normal and reconverted marrow. If signal loss is less than 20%, there is a higher chance of a benign or malignant lesion in the affected marrow [22,23]. Also, healed neoplastic lesions often have intra- or perilesional fatty signal intensity which may have a similar appearance on conventional imaging. Dixon and chemical shift techniques are capable of detecting fat signal in the lesions or at the periphery and avoid misinterpretation of inactive as active lesions, and impact patient management.

Functional Imaging

Diffusion-weighted Imaging

Diffusion-weighted imaging (DWI) is a method that generates signal contrast based on the differences in Brownian motion of the tissue molecules [24]. Water diffusion in biological tissues is restrained by cellular membranes, organites and macromolecules, and in a general sense, highly cellular tissues exhibit lower diffusion coefficients. Apparent diffusion coefficient (ADC) is a quantitative biomarker of diffusion, more specifically a magnitude of diffusion of water molecules in a certain tissue and is calculated based on DW images. ADC histograms / parametric maps have been used in several tumors in different organs, namely pancreas, kidney, adrenals, uterus and, also, in MM [25,26]. Diffusion signal is decreased in yellow marrow and increased in red marrow due to higher vascularization and water content. But, more importantly, DWI is helpful in distinguishing red cellular marrow (less hyperintense on DWI and T2-shine through effect) from a suspicious bone lesion (more hyperintense on DWI with ADC restriction).

ADC behavior can make the distinction of a benign from a malignant lesion (the former having increased ADC enhancement). Bone marrow infiltration with MM cells creates a high diffusion signal due to replacement of yellow marrow adipocytes and increased cellular density. A focal lesion is defined as a lesion with low T1-weighted signal and high T2-weighted signal. Diffuse disease is described as diffuse bone marrow hypointense signal on T1WI and diffuse high signal on T2WI [27]. Care should be taken in the presence of chondroid, myxoid, hemorrhagic and sclerotic bone lesions, however, which behave differently. In this respect, diffusion-weighted whole-body MRI (DW-WBMRI) has been used to screen bone marrow diseases, monitor and predict tumor response to therapy.

Dynamic Contrast-Enhanced MRI

Post-contrast administration imaging can provide functional information on bone marrow infiltration. Dynamic contrast-enhanced whole-body MRI (DCE-WBMRI) captures the signal intensity throughout different time periods after intravenous contrast administration and computation of time-signal intensity curves provide signal maps with distinct patterns that may be correlated to higher or lower amounts of plasma cell infiltration. DCE-WBMRI has been shown to have a positive correlation with MM activity and serum biomarkers [28] and predicts rapid progression from smoldering MM (SMM) to symptomatic disease [29]. Treatment response may also be evaluated with DCE MRI, in which persistence of elevated peaks of marrow enhancement and foci of early enhancement are correlated with poor treatment response [30]. Specific time-signal curves have also been associated with high cellularity in whole spine perfusion in MM patients, and better correlate with viable malignancy [31] (Figure 1).

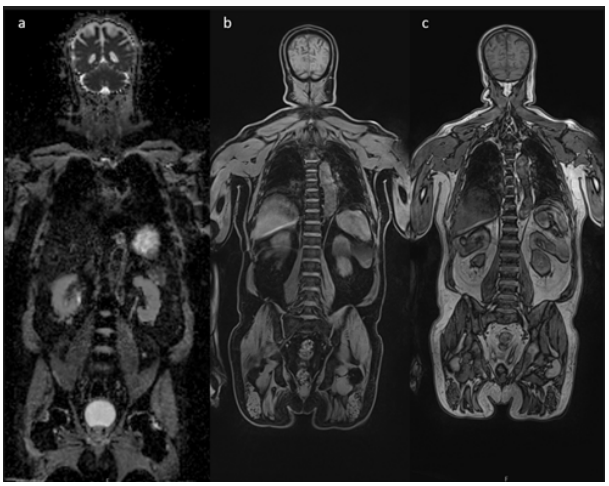

Figure 1: 75-year-old male patient with MM, whole-Body MRI, coronal plane

a. ADC map

b. DIXON water-only sequence

c. Dixon out-of-phase sequence

^{18}F-FDG-PET / MRI

A new hybrid technology combining PET and MRI has the potential to detect bone and extramedullary lesions through simultaneous metabolic and anatomic information [32]. Some studies have shown that ^{18}F-FDG-PET / MRI has the ability to detect medullary compression and bone lesions in patients with newly diagnosed SMM and newly diagnosed MM, with a higher diagnostic performance for MRI which detected focal lesions in 30% and 22% of PET-negative examinations [33]. Jamet et al. also detected a higher performance of MRI in SMM compared to PET [9]. ^{18}F-FDG-PET / MRI has also been reported to have higher lesion detectability rates compared to 18F-FDG-PET / CT in skeletal lesions [34] while other authors concluded that they are equally sensitive [35].

Other Techniques

Proton magnetic resonance (1H-MRS) spectroscopy is a non-invasive technique that detects and quantifies compounds or metabolites in tissue and has been tried out in MM. 1H-MRS spectroscopy determines the concentration of specific metabolites and its main applications in bone marrow evaluation are related to fat quantification [36]. Intravoxel incoherent motion MRI uses low b-value (<300 s / mm2) DWI to acquire perfusion maps without the need for intravenous contrast injection. Its usefulness in clinical practice is still not validated [37,38], but it seems promising for MM as it has been established that patients with newly diagnosed MM show increased bone marrow vascularity [39,40] and frequent kidney involvement in such patients may hinder the applicability of DCE MRI [38].

Deep Learning Applications

Several machine learning and deep learning algorithms have been developed for MM diagnosis and workup [41]. Artificial intelligence algorithms are able to establish correlations with large groups of data and boost research on serology, histology, radiology and genetic data. Several studies have explored the role of computational systems and their capabilities for clinical and laboratory diagnosis, and a few have tackled imaging modalities. Xu et al. and Mesguich et al. have analyzed PET-CT images with deep learning and machine learning techniques resorting to radiomics with interesting results [42,43]. Interestingly, Xiong et al. was able to differentiate MM and metastasis subtypes of lumbar vertebra lesions with a machine learning radiomics algorithm [44].

Future Directions

Several novel imaging techniques are being employed for MM with promising results not only in early diagnosis but also in functional assessment and response to therapy. MRI is making steady progress and gaining ground due to its sensitivity for early diagnosis, the ability to make a non-invasive evaluation of disease activity and treatment response prone to cause a significant impact in clinical practice, without exposure to ionizing radiation. With the development of new techniques and sequences, with increased resolution and faster acquisition times that can be improved upon with artificial intelligence, it is only conceivable that MRI will get increasingly more attention and utility for MM patients over time in every stage of the disease.

Conflicts of Interest

The authors declare no conflicts of interest.

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