International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 6, No. 1, 2024

The Current Research Status of Imaging Assessment of Bone Disease in Multiple Myeloma

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Abstract: With rapid advancements in the diagnosis and treatment of bone disease in multiple myeloma (MBD), Imaging assessments play a crucial role in the diagnosis and management of MBD. Traditional whole-body X-ray has been commonly used. Whole-body low-dose computed tomography, whole-body MRI, and 18F-FDG PET/CT are more sophisticated techniques that have been recommended for the initial assessment of MM-related lytic bone lesions. MRI remains the gold standard for bone marrow involvement detection, while PET/CT offers valuable prognostic data and is preferred for therapy response assessment. Diffusion-weighted MR has been shown to be superior to both skeletal X-ray and MRI of the spine for detecting focal lesions in MBD. Diffusion-weighted MR is a functional imaging technique that effectively detects bone disease changes according to treatment response and can be used to monitor disease response. Advanced imaging techniques have significantly improved the sensitivity for detecting MBD. This review focuses on the imaging modalities available for MBD patient management, highlighting advantages, disadvantages, and applications of each.

Keywords: Image; MBD; Evaluate.

1. Introduction

The Multiple myeloma (MM) is a complex hematological malignancy characterized by the uncontrolled proliferation of clonal plasma cells within the bone marrow, often leading to the production of monoclonal immunoglobulins detectable in serum or urine[1]. This disease is the second most common hematological cancer, representing about 1% of all cancers and 13% of hematological tumors[2]. MM typically presents with bone marrow infiltration by clonal plasma cells and is diagnosed when there is clear evidence of end-organ damage or a high likelihood of its development[3].Recent therapeutic advances have significantly improved patient outcomes. The introduction of novel drugs, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies targeting CD38, has extended survival, although the disease remains incurable for most patients[1]–[3]. The management of MM involves a combination of treatments, including high-dose chemotherapy, autologous stem cell transplantation, and targeted therapies[3]. Current clinical research is focused on balancing treatment efficacy with quality of life, optimizing the sequencing of treatments, achieving long-term remission, preemptive treatment of high-risk SMM, and the role of maintenance therapy[1]. The use of minimal residual disease assays to guide therapy, refining immunotherapeutic approaches, and intercepting disease early in SMM are among the strategies being investigated[4].

A significant complication of MM is bone disease, which is present in the majority of patients and can lead to a range of skeletal-related events (SREs) such as fractures, spinal cord compression, and severe bone pain, thereby reducing the quality of life and increasing mortality risk[5]–[7]. The pathogenesis of MM bone disease (MBD) involves an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts, leading to the development of osteolytic lesions that do not heal even when the myeloma is in remission[6], [7].Current therapeutic strategies for MBD include the use of bisphosphonates and the RANKL inhibitor denosumab, which have been shown to delay SREs and reduce the need for surgery or radiation therapy[5], [8]. However, these treatments do not fully repair existing bone lesions.

Imaging plays a crucial role in the diagnosis, staging, and treatment monitoring of MM, particularly in the assessment of bone disease. Whole-body low-dose computed tomography (WBLDCT) is now the preferred method for detecting osteolytic bone lesions, which are a hallmark of MM[9]. Magnetic resonance imaging (MRI) offers superior soft-tissue contrast and is the gold standard for evaluating bone marrow involvement, crucial for early detection of marrow infiltration by myeloma cells[10]. Positron emission tomography/computed tomography (PET/CT) provides both functional and morphological information, making it valuable for assessing disease activity and treatment response[9], [11].

Therefore, imaging has gained an increasingly important role in diagnosis, prognostication, and assessment of therapeutic efficacy in MBD. Imaging modalities such as WBLDCT, MRI, and PET/CT are integral to the management of MM, each with its own set of advantages for different clinical scenarios. The choice of imaging technique is guided by the need for detailed bone lesion assessment, bone marrow evaluation, and functional assessment of disease activity and response to therapy. This review will focus on the various imaging modalities available for MBD patient, highlighting advantages, disadvantages, and applications of each.

2. Methods

2.1. Conventional Radiographic Skeletal Survey

The radiographic skeletal survey(X-rays) is a traditional imaging technique used to detect bone disease in patients with MM. It involves taking a series of X-rays to visualize the entire skeleton, aiming to identify lytic lesions, fractures, and other signs of myeloma bone disease. However, the

diagnostic performance of X-rays has been challenged by more advanced imaging techniques.

One of the main characteristics of X-rays is its high specificity, as reported in a study where X-rays had a specificity of 83±1% for detecting bone destruction in smouldering MM[12]. Despite this, X-rays has a relatively high false-negative rate, meaning it may not detect all areas of bone disease[12]. This limitation is particularly evident when compared to positron emission tomography/computed tomography (PET/CT) with 18F-fluorodeoxyglucose (FDG), which has been shown to be superior in detecting bone lesions, including in cases where X-rays results are negative[13].

Another characteristic of X-rays is its ability to detect typical radiographic associations of features and sites, which can sometimes make diagnosis easier[14]. The most frequent lesions identified by X-rays are osteopenia and osteolysis, with the spine, skull, pelvis, ribs, humeri, femora, and mandible being the most commonly involved locations[14]. However, X-rays is less sensitive than other imaging modalities like MRI and PET/CT, which can detect bone marrow involvement and bone destruction not visible on X-rays[13].

The advantages of SS include its widespread availability, low cost, and the ability to survey the entire skeleton. However, its disadvantages include low sensitivity for early bone marrow involvement, inability to detect soft tissue masses, and exposure to ionizing radiation[15]. Moreover, X-rays may not be as effective in monitoring therapeutic response as other techniques like MRI or PET/CT[16].

In conclusion, while X-rays remains a tool for the initial evaluation of bone disease in MM, its limitations necessitate the use of more sensitive imaging techniques, such as MRI and PET/CT, for comprehensive assessment and monitoring of the disease[13]. These advanced imaging modalities can provide additional valuable information, particularly in areas not covered by SS, and are more effective in assessing response to therapy[16].

2.2. WBLDCT

Whole-body low-dose computed tomography (WBLDCT) has emerged as a significant diagnostic tool for the assessment of bone lesions in patients with MM.

WBLDCT is characterized by its ability to detect bone marrow localizations and demonstrate extra-osseous findings with high-resolution images and fast scanning times. It has been shown to detect a total of 328 pathologic bone findings in a study of 138 patients, with an overall dose delivered to each patient being 4.2 mSv[17]. The diagnostic value of WBLDCT is also highlighted by its superior detection rate for lytic bone lesions compared with whole-body X-ray (WBXR), potentially leading to restaging and changes in therapy[18].

One of the main advantages of WBLDCT is its higher sensitivity and specificity compared to skeletal surveys in detecting osteolytic lesions. It has been shown to identify more lesions with greater diagnostic confidence and has led to restaging in several instances[19]. WBLDCT also provides complementary information to whole-body magnetic resonance imaging (WBMRI) in patients with normal marrow signal following treatment response[19]. Furthermore, WBLDCT has been found to be a reproducible and reliable technique with good inter-observer agreement, even when comparing different protocols[20].

Despite its advantages, WBLDCT has some limitations. There can be variability in the evaluation of hyperattenuating lesions and the presence of fractures[20]. Additionally, while WBLDCT is effective in detecting changes in the course of the disease, there can be moderate agreement with hematologic analysis at the time of investigation, with CT being correct in 60% of mismatching cases[21].

WBLDCT is applicable in various clinical settings, including staging, follow-up, therapy monitoring, and evaluation of stability in MM patients. It is particularly useful in the detection of spinal involvement, offering detailed information about extra-axial involvement that could be potentially missed with dedicated spinal MRI[22]. The technique is also beneficial for patients with nonsecretory MM, where it can assess the course of the disease correctly7. Moreover, WBLDCT can exclude the presence of myeloma bone disease in patients with monoclonal gammopathy of undetermined significance (MGUS), complementing hematologic laboratory analysis[23].

In conclusion, WBLDCT is a valuable imaging modality for the evaluation of bone disease in MM patients, offering advantages over traditional imaging techniques. Its use should be considered in the appropriate clinical context, taking into account its limitations and the specific conditions of the patient.

2.3. Dual-energy CT (DECT)

Dual-energy CT (DECT) has emerged as a valuable imaging modality for the assessment of bone disease in patients with MM. DECT utilizes two different energy spectra to acquire images, allowing for advanced tissue characterization and the ability to differentiate and subtract specific materials, such as calcium, from the scan. This capability is particularly useful in evaluating bone marrow infiltration in MM, where conventional imaging may be limited.

The characteristics of DECT in assessing MM bone disease include high diagnostic accuracy, as demonstrated by the virtual noncalcium (VNCa) technique. This technique has shown excellent sensitivity and specificity in detecting bone marrow infiltration, with performance comparable to magnetic resonance imaging (MRI)[24]. DECT-based bone marrow imaging can also differentiate between active and inactive disease states in MM by assessing focal osteolytic lesions, with attenuation measurements correlating with disease activity[25].

Advantages of DECT include its ability to provide additional information on tissue composition, which is beneficial for detecting urate and bone marrow edema, reducing metal artifacts, and optimizing images for various clinical applications[26]. DECT has also shown excellent sensitivity and specificity for detecting bone marrow edema, which is a common finding in MM[27].

However, DECT has some limitations. The technique requires specialized equipment and software, and there may be a learning curve associated with interpreting the advanced imaging results. Additionally, the radiation dose, while comparable to conventional CT, is a consideration, especially in patients requiring multiple follow-up scans.

DECT is suitable for patients with MM, particularly when MRI is contraindicated or unavailable. It is also useful for monitoring treatment response, as changes in textural features on DECT-derived bone marrow images correlate with hematologic parameters and can provide complementary information for assessing the effects of treatment on bone marrow[28].

In conclusion, DECT is a powerful tool for the evaluation of bone disease in MM, offering high diagnostic accuracy and the ability to monitor disease activity and treatment response. Its use should be considered in the context of the patient's overall clinical picture and in facilities equipped with the necessary technology.

2.4. PET/CT

Positron Emission Tomography-Computed Tomography (PET/CT) is a hybrid imaging technique that combines the functional imaging capabilities of PET with the anatomical detail provided by CT. In the context of MM, PET/CT is particularly useful for evaluating the extent of bone disease, which is a common and clinically significant feature of MM.

PET/CT imaging in MM typically involves the use of 18F-fluorodeoxyglucose (FDG), a radiolabeled glucose analog. Cancer cells, including myeloma cells, have a higher metabolic rate than normal cells and therefore take up more FDG. The PET component of the scan detects the radiation emitted by FDG, allowing for the visualization of areas with increased glucose metabolism, which often correspond to sites of active disease. The CT component provides detailed anatomical information, enabling precise localization of the lesions detected by PET[29]–[35].

PET/CT has several advantages in the assessment of MM bone disease. It can detect both medullary and extramedullary involvement, assess disease burden, and identify bony lesions that may not be visible on conventional radiography[30], [31], [33]. PET/CT is also valuable for prognostication, as the presence and number of focal lesions (FLs) and extramedullary disease (EMD) detected by PET/CT have been associated with survival outcomes[30], [32], [35]. Additionally, PET/CT can be used to monitor therapeutic response, with studies showing that normalization of PET/CT findings after treatment correlates with improved progression-free survival (PFS) and overall survival (OS)[32], [35].

Despite its benefits, PET/CT also has limitations. It may not detect all sites of disease, particularly when compared to whole-body MRI, which is considered the gold standard for detecting bone marrow involvement[13], [34]. Furthermore, PET/CT involves exposure to ionizing radiation, which is a consideration for patients undergoing repeated scans[33].

PET/CT is particularly applicable in the initial staging of MM, assessment of disease burden, and evaluation of response to therapy, including before and after stem cell transplantation[29], [32], [35]. It is also useful in cases where MRI is contraindicated or not available, and in the detection of EMD, which has significant prognostic implications[31], [34], [35].

In conclusion, PET/CT is a powerful tool in the evaluation of MM bone disease, offering both functional and anatomical information that can guide diagnosis, prognostication, and treatment decisions. However, its use should be considered in the context of other imaging modalities and individual patient factors.

2.5. MRI

Magnetic Resonance Imaging (MRI) has become an essential tool in the assessment of bone disease in patients with MM, offering several advantages over traditional radiographic methods. MRI is highly sensitive for the early detection of marrow infiltration by myeloma cells, which allows for the detection of bone involvement much earlier than myeloma-related bone destruction becomes apparent on X-rays[10]. It is considered the gold standard for imaging the axial skeleton, evaluating painful lesions, and distinguishing between benign and malignant vertebral fractures[10].

The principle behind MRI in evaluating MM bone disease lies in its ability to detect changes in the bone marrow environment caused by the infiltration of myeloma cells. MRI can reveal different patterns of bone marrow involvement, such as focal, diffuse, or variegated (salt-and-pepper) patterns, which are indicative of the disease's presence and extent[36].

One of the key advantages of MRI is its ability to visualize the entire bone marrow compartment without the use of ionizing radiation. This makes it particularly useful for the evaluation of the spine and pelvis, which are common sites of MM involvement[13]. MRI can also detect spinal cord or nerve compression and the presence of soft tissue masses, which are critical for patient management[10].

However, MRI does have limitations. It may not detect myelomatous lesions in areas outside of its field of view, and it is less effective in identifying extramedullary disease[13]. Additionally, MRI is not as widely available as other imaging modalities, can be more expensive, and the examination can be time-consuming[10].

Despite these limitations, MRI is recommended for the workup of solitary bone plasmacytoma and is considered a valuable tool for the assessment of therapeutic response, especially after treatments such as autologous stem-cell transplantation. It provides prognostic information, although it does not currently change treatment selection[10].

In the context of minimal residual disease (MRD), MRI, along with PET-CT, is being explored as a strategy to overcome the limitations of traditional methods that rely on bone marrow biopsies and serum markers. These imaging modalities can provide a more comprehensive assessment of disease status, including the detection of MRD[37].

In conclusion, MRI is a powerful imaging modality for the assessment of bone disease in MM patients. It offers high sensitivity for early detection, excellent soft-tissue contrast, and the ability to evaluate the axial skeleton comprehensively. While it has some limitations and may not replace other imaging techniques entirely, MRI is an invaluable part of the diagnostic and monitoring arsenal for MM bone disease.

2.6. DW-MRI

Whole-body diffusion-weighted MRI (DW-MRI) is a non-invasive imaging technique that has been increasingly utilized for the assessment of bone disease in MM. The principle behind DW-MRI is based on the measurement of the Brownian motion of water molecules within tissues. In the context of MM, the presence of malignant plasma cells in the bone marrow alters the normal tissue architecture and affects the diffusion of water molecules. This change in diffusion can be quantified using the apparent diffusion coefficient (ADC), which is a parameter derived from DW-MRI images.

The main advantage of DW-MRI is its ability to provide both anatomical and functional information about bone lesions without the need for ionizing radiation or intravenous contrast agents. This makes it particularly useful for patients who are unable to undergo contrast-enhanced studies or who require repeated imaging for monitoring disease progression or response to therapy[38]–[43].

One of the key features of DW-MRI is its high sensitivity in detecting diffuse bone marrow infiltration and focal lesions,

which are characteristic of MM. Studies have shown that DW-MRI can detect more focal lesions compared to conventional radiography and has a high concordance with the bone marrow plasma cell infiltration rate[36], [38]. Additionally, changes in ADC values post-treatment have been correlated with response to chemotherapy, with responders showing a significant increase in ADC values, indicating a reduction in cellularity and a positive treatment effect[39], [44].

However, DW-MRI also has some limitations. The interpretation of images can be challenging due to the presence of artifacts, and there is a need for standardization in image acquisition and analysis. Moreover, the technique may be less effective in detecting lesions in certain areas of the body, such as those with complex anatomy or where motion artifacts are more prevalent[45], [46].

In terms of applicability, DW-MRI is particularly suited for patients with MM who require a comprehensive evaluation of bone disease, including those who are undergoing chemotherapy and need to be monitored for treatment response. It is also valuable for patients who cannot be exposed to radiation or contrast agents[40], [41], [43].

In conclusion, whole-body DW-MRI represents a complementary diagnostic tool in the management of MM, offering a sensitive method for detecting bone lesions and monitoring treatment response. Its non-invasive nature and functional imaging capabilities make it a promising modality for improving patient care in MM.

3. Results

3.1. Applications to Clinical Practice

In the clinical application for assessing bone disease in MM, the selection of appropriate imaging techniques is critical and should be tailored to the specific clinical scenario. The choice of imaging modality can be influenced by factors such as the stage of the disease, the need for whole-body assessment, the presence of extramedullary disease, and the evaluation of treatment response.

For initial staging and assessment of bone disease extent, 18F-FDG PET-CT and MRI have been shown to have higher sensitivity and specificity than whole-body X-ray. 18F-FDG PET-CT is particularly useful for identifying extramedullary disease and has prognostic value at staging, while MRI is the most sensitive technique for detecting diffuse bone marrow involvement.

DW-MRI has been identified as superior to skeletal X-ray , MRI of the spine, and conventional whole-body MR in detecting focal lesions in MM. DW-MRI is also effective in monitoring disease response to treatment, as it can detect significant changes in focal lesions according to disease response.

When comparing 18F-FDG PET/CT with 99mTc-MIBI scintigraphy and MRI, 18F-FDG PET/CT has been found to perform better in the detection of focal lesions, while 99mTc-MIBI is superior in visualizing diffuse disease. MRI is comparable to both in the detection of focal and diffuse disease in the spine and pelvis.

In cases where MRI of the spine and pelvis is the focus, 18F-FDG PET-CT provides additional valuable information for the assessment of myeloma bone disease in areas not covered by MRI. Combining MRI of the spine-pelvis and 18F-FDG PET-CT can detect active MM sites at a high rate.

For the assessment of imaging response, whole-body MRI (WB-MRI) and 18F-FDG PET-CT have emerged as sensitive techniques. WB-MRI may be superior for assessing the extent of lesions, while PET/CT is better for monitoring disease activity and detecting asymptomatic relapse.

WBLDCT, WB-MRI, and 18F-FDG PET-CT are recommended for different settings in MM management. WBLDCT is preferred for initial assessment of MM-related lytic bone lesions, MRI for bone marrow involvement, and PET/CT for response to therapy.

Extended Texture Analysis of Non-Enhanced Whole-Body MRI has been used to identify radiomics features capable of assessing response to systemic treatment in MM patients. This technique can provide significant information to assess clinical and hematological response.

Lastly, DECT with a virtual noncalcium (VNCa) technique has shown excellent diagnostic performance for assessing bone marrow infiltration, comparable to that of MR imaging.

In conclusion, the selection of imaging techniques in MM should be based on the specific clinical needs of the patient. 18F-FDG PET-CT and MRI are generally preferred for initial assessment and staging, DW-MR for detecting FL and monitoring treatment response, and a combination of MRI and PET/CT for comprehensive evaluation. Advanced techniques such as WB-MRI and DECT can provide additional valuable information for treatment response and minimal residual disease assessment.

4. Conclusion

Imaging assessment of MBD has evolved significantly, with various modalities offering distinct advantages. the current state of imaging assessment in MBD involves a multimodal approach, with MRI, PET/CT, and advanced CT techniques each playing a critical role in diagnosis, prognosis, and monitoring of treatment response. These imaging modalities provide a more comprehensive assessment of bone lesions and are instrumental in staging the disease, guiding treatment decisions, and evaluating therapeutic responses.

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