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Multiple Myeloma: Role of Imaging in Diagnosis, Staging, and Treatment Response Assessment

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Multiple myeloma is a common hematologic malignancy of plasma cells. Differentiating multiple myeloma from the precursor stages of monoclonal gammopathy of undetermined significance and smoldering multiple myeloma is very important because the treatment approach is different for each. The diagnosis is mainly clinical, while the role of imaging is confined to the staging process, assessing response to therapy, and monitoring for disease progression. In this article, we examine the role of different imaging modalities in patients with multiple myeloma.
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Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States.[1] It is a malignant neoplasm of differentiated plasma cells that results from malignant clonal proliferation of plasma cells. The malignant plasma cells reside primarily in the bone marrow. However, in advanced stages of the disease, they could invade the peripheral blood and other extra-medullary sites like soft tissues and organs.[2] In the majority of patients, malignant proliferation of plasma cells results in the production monoclonal immunoglobulins (also known as M-protein or monoclonal proteins) in the serum and/or urine. Immunoglobulin G (IgG) is the most commonly secreted monoclonal protein and is found in approximately 60% of patients, followed by IgA, secreted in 20% of cases.[3] However, 15%-20% of patients secrete light chains as the sole monoclonal protein. Less than 3% of patients have nonsecretory disease when malignant plasma cells secrete no monoclonal proteins. However, the percentage of the nonsecretory disease has declined recently owing to an improved ability to detect serum free light chains.[3-5]

Incidence

MM is the second most common hematologic malignancy in the United States after non-Hodgkin lymphoma with an approximate annual incidence of 32,110 patients, with slight male predominance (1.3:1).[1] Typically, MM occurs in the elderly, most commonly during the seventh and eighth decades of life, with a median age at onset of 66 years.[4] The incidence rate is 2-3 times higher in the African American population compared to the Caucasian population. The explanation for that difference is still unknown, but the precursor, monoclonal gammopathy of undetermined significance (MGUS), is also more common among the African American population.[6,7]

Etiology

The exact etiology of MM is still unclear. However, numerous environmental, occupational, and genetic factors have been implicated. Chronic exposure to low-dose ionizing radiation, such as occurred in radiologists and radiology technicians before the routine use of shielding, is associated with increased risk of MM. Additionally, exposure to chemical

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materials from working in the leather tanning, pulp, and paper industries has been linked to an increased risk of MM.[8] Recently, several reports have suggested an association between increased incidence of MM and MGUS among certain populations with certain chromosomal and cytogenetic abnormalities.[9]

Pathology

MM results from the monoclonal expansion of malignant plasma cells. Cells of plasmacytic origin are usually positive for CD38 and CD138, while negative for other markers of B-cell lineage like CD19 and CD20.[10] Numerous chromosomal and cytogenetic abnormalities have been linked to the development of MM, and to the progression of precursor disease states such as smoldering MM (SMM) and MGUS into MM. SMM is an intermediate state between MGUS and MM, with an approximate annual risk of progressing to MM of 10%.[11] The most common chromosomal abnormalities include chromosomal defects such as chromosome 1 abnormalities, deletion of the long arm of chromosome 13 (13q) and the loss of the short arm of chromosome 17 (17p). Also seen are chromosomal translocations such as t(11;14) which is found in 14% of patients, and translocation t(4;14) which is found in 11% of patients. The translocations t(11;14) and t(4;14) are associated with a shorter time to progression from SMM to MM, with a median time of 55 months and 28 months, respectively.[10,12]

Clinical Presentation

MM is often diagnosed incidentally during routine work-up. The clinical picture is variable, and patients with MM could present with a number of characteristic clinical features, and sometimes, complications. However, the majority of patients present with bone pain and fatigue. Bone pain is the most common initial presentation, occurring in up to 80% of patients at the time of diagnosis, and is often associated with lytic bone lesions.[13] The lytic lesions of MM are caused by an imbalance in the activity of bone producing osteoblasts and bone resorbing osteoclasts, resulting in progressive bone destruction and development of lytic foci.[14] In advanced stages, progressive bone destruction results in hypercalcemia which occurs in approximately 20% of patients. Fatigue results from bone marrow infiltration leading to development of normocytic normochromic anemia in approximately 75% of patients.[4,15] MM may present with complications such as hypercalcemia, blood hyperviscosity caused by high levels of circulating monoclonal proteins in the serum, frequent infections due to impaired immune response, and renal failure. Renal failure is the most common complication, and is experienced by approximately 50% of patients at some time during their disease course. Renal failure commonly occurs due to cast nephropathy caused by the accumulation of obstructing casts of light chains and Tamm-Horsfall urinary glycoprotein in the distal tubule.[16,17]

Diagnosis

MGUS and SMM are generally asymptomatic, and are usually discovered during the diagnostic work-up for unrelated conditions.[18] Therefore, the International Myeloma Working Group (IMWG) devised updated criteria for the diagnosis of MM and for differentiating it from MGUS and SMM (Fig. 1). This distinction is needed because of the different treatment approaches in each.[18] These diagnostic criteria are based on bone marrow biopsy, measurement of serum monoclonal

International Myeloma Working Group (IMWG) updated diagnostic criteria for multiple myeloma (18).

Both criteria must be met:

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma.
- Presence of one or more of myeloma defining events (MDEs).

Myeloma defining events (MDEs) include the following:

- CRAB features (see below).
- Clonal bone marrow plasma cell (BMPC) percentage ≥60%.
- Involved: uninvolved serum free light-chain (FLC) ratio ≥100.
- Two or more focal lesions on MRI (at least 5 mm in size).

CRAB features include the following:

- Hypercalcemia: serum calcium >1 mg/dl higher than the upper limit of normal or >11 mg/dl.
- Renal insufficiency: serum creatinine >2 mg/dl or creatinine clearance <40 ml/min.
- Anemia: hemoglobin level >2 g/dl lower than the lower limit of normal or serum hemoglobin value <10 g/dl.
- Bone lesions: one or more lytic lesions on conventional radiography, CT or PET/CT.

Figure 1 International Myeloma Working Group (IMWG) updated diagnostic criteria for multiple myeloma.[18]

proteins, and screening for the presence of myeloma-defining events. Myeloma-defining events include biomarker assessment and detection of CRAB features. CRAB features are used to determine the presence or absence of end-organ damage, and include hyper**C**alcemia (increased serum calcium levels >1 mg/dL above upper normal limits), **R**enal insufficiency (serum creatinine levels of >2 mg/dL or creatinine clearance of <40 mL/min), **A**nemia (decreased hemoglobin levels >2 g/dL below lower normal limits), and detection of one or more lytic **B**one lesions by conventional radiology, computed tomography (CT) or positron emission tomography/CT (PET/CT), or the detection of 2 or more focal bone lesions by MRI (at least 5 mm in size). Malignancy biomarkers include a clonal bone marrow plasma cell percentage of ≥60% or an involved:uninvolved serum free light-chain ratio of ≥100%.[18]

Staging

Numerous staging systems have been established to determine disease progression and predict prognosis in patients with MM. In 1975, Durie and Salmon initiated the first staging system based on multiple parameters including hemoglobin levels, serum calcium levels, and renal function to predict the volume of myeloma tumor mass.[19] This system became the standard staging system for several decades (Fig. 2). However, this system lacked precision as multiple parameters such as the degree of anemia, hypercalcemia, and renal impairment could be affected by other factors unrelated to myeloma progression. Additionally, the emergence of new prognostic factors such as cytogenetic abnormalities, albumin levels, and beta-2 microglobulin (β_2M) necessitated the need for developing a new staging system. Therefore, in 2005, Greipp et al developed the International Staging System based on serum albumin and beta-2 microglobulin (β_2M) levels[20] (Fig. 3). This system categorized MM patients into 3 stages predicting their median survival time, and became the standard staging system. Later on, realizing the significant impact of chromosomal abnormalities on prognosis and the emergence of new novel agents, Palumbo et al developed the Revised International Staging System by incorporating the chromosomal abnormalities into the standard International Staging System to predict prognosis and 5-year overall survival rates[21] (Fig. 4). They classified patients into 2 groups including a high-risk group characterized by the presence of high-risk chromosomal abnormalities including deletion of chromosome 17 del(17p), translocations t(4;14) and t(14;16), and standard-risk group characterized by the absence of high-risk chromosomal abnormalities.

Imaging

Imaging helps to distinguish MM from SMM, MGUS, and solitary plasmacytoma. Imaging enables us to identify focal bone lesions and provides information regarding their number, size, and location. Once the diagnosis is established, imaging plays a role in the staging process, screening for disease progression, risk stratification, and estimating the risk of

Durie and Salmon Staging System (19)

Stage	Myeloma Cell Mass ($\times 10^{12}/m^2$)
Stage I (all are needed for diagnosis)	
Hemoglobin level: >10 g/100 ml	
Serum calcium level: normal or ≤12 mg/100 ml	
X-ray: normal or solitary plasmacytoma	Low (<0.6)
Low production rates of M-component: IgG <5 g/100 ml, IgA <3 g/100 ml	
Urine light chain M component: <4 g/24 hours	
Stage II	
Neither stage I nor III	Intermediate (0.6-1.2)
Stage III (one or more are needed for diagnosis)	
Hemoglobin level: <8.5 g/100 ml	
Serum calcium level: >12 mg/100 ml	
X-ray: >3 lytic lesions	High (>1.2)
High production rates of M-component: IgG >7 g/100 ml, IgA >5 g/100 ml	
Urine light chain M component: >12 g/24 hours	

**Each stage is sub-classified into either group A with normal renal functions (serum creatinine level <2 mg/100 ml), or group B with impaired renal functions (serum creatinine ≥ 2 mg/100 ml).*

Figure 2 Durie and Salmon Staging System.[19] *Each stage is subclassified into either group A with normal renal functions (serum creatinine level <2 mg/100 mL), or group B with impaired renal functions (serum creatinine ≥2 mg/100 mL).

International Staging System (ISS), (20)

Stage*	Survival (months)
Stage I	
β_2M <3.5 mg/l and albumin ≥3.5 g/dl	62
Stage II	
β_2M 3.5-5.5 mg/l irrespective of albumin level or β_2M <3.5 mg/l and albumin <3.5 g/dl	44
Stage III	
β_2M ≥5.5 mg/l	29

Abbreviations: β_2M; beta-2 microglobulin

**Serum levels*

Figure 3 International Staging System (ISS).[20] β_2M, beta-2 microglobulin. *Serum levels.

pathologic fracture. Lytic bone lesions are not associated with new bone formation; therefore, skeletal scintigraphy is not typically helpful.[22]

Conventional Radiography

For decades, skeletal surveys have been the mainstay of imaging in MM and were integrated in the original Durie and Salmon staging system.[19] Skeletal surveys are usually obtained as part of the initial diagnostic work-up in patients with MM and this whole-body x-ray (WB-XR) remains the gold standard technique to evaluate MM-related bone disease.[23] However, the presence of lytic bone lesions on skeletal surveys necessitates the use of more advanced modalities. Lytic lesions appear as either well-defined, punched-out lesions, sometimes with endosteal scalloping, or ill-defined lucencies representing the replacement of bone marrow with expanding plasma cell populations that induce subsequent bone destruction[24] (Fig. 5). A 15-view approach has been suggested by the IMWG including: skull anteroposterior (AP) and lateral; cervical spine AP, open-mouth odontoid and lateral; thoracic spine AP and lateral; lumbar spine AP and lateral; pelvis AP; chest AP; femora AP and lateral; and humeri AP and lateral.[23] While skeletal surveys can detect the presence of lytic bone lesions, at least 30%-50% loss of bone mineralization is necessary for the lesions to be visible on radiographs depending on bone type and location of the lesion within the bone.[25,26] Skeletal surveys are widely available, relatively inexpensive and can provide an assessment for the risk of pathologic fracture (Fig. 6). Additionally, they can be useful in detecting disease progression[27] (Fig. 7). However, they have major limitations such as limited visualization of the pelvis and spine due to overlapping structures,

Revised International Staging System (R-ISS). (21)

Stage	Frequency (% of patients)	5-year survival rate (%)
Stage I		
ISS stage I and No high-risk CA and Normal LDH	28	82
Stage II		
Neither stage I nor III	62	62
Stage III		
ISS stage III and Either high-risk CA or high LDH	10	40

Abbreviations: ISS; International staging system, CA; chromosomal abnormalities, LDH; lactate dehydrogenase.

Figure 4 Revised International Staging System (R-ISS).[21] ISS, International Staging System; CA, chromosomal abnormalities; LDH, lactate dehydrogenase.

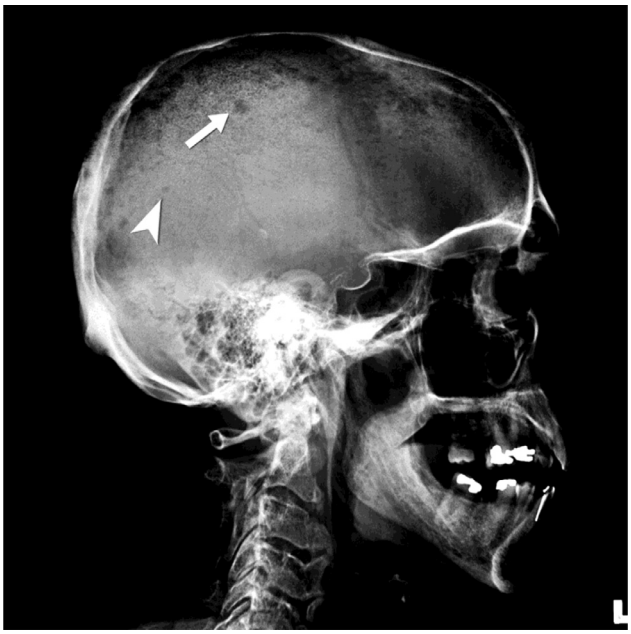

Figure 5 Sixty-eight-year-old male with high-risk multiple myeloma. The patient is in complete remission following induction chemotherapy. He will proceed with autologous stem cell transplantation. Radiograph of the skull, lateral view, shows multiple small lytic lesions scattered throughout the calvarium despite complete response to therapy. Most lytic myelomatous lesions are well defined (arrowhead), but some can be ill-defined (arrow). While the lesions may or may not fade over time, sclerotic rims infrequently occur around treated lesions due to suppression of osteoblast activity.

inability to detect extraosseous lesions, and limited utility in assessing the response to treatment because the lytic lesions heal very slowly on radiographs,[26] if at all. Moreover, WB-XR is not suitable for detection of MM-related osteoporosis.[23]

Computed Tomography

The use of low-dose whole-body CT has been suggested as an alternative to skeletal survey, owing to higher sensitivity, especially for lesions located in the ribs, pelvis, or spine.[28,29] CT can detect smaller lytic bone lesions not detectable on conventional radiography, and provide an assessment for the risk of pathological fracture[29,30] (Fig. 8). Additionally, CT can be useful for detection of complications.[31] However, CT has low sensitivity for detecting bone marrow lesions and diffuse marrow infiltration not associated with lytic reactions.

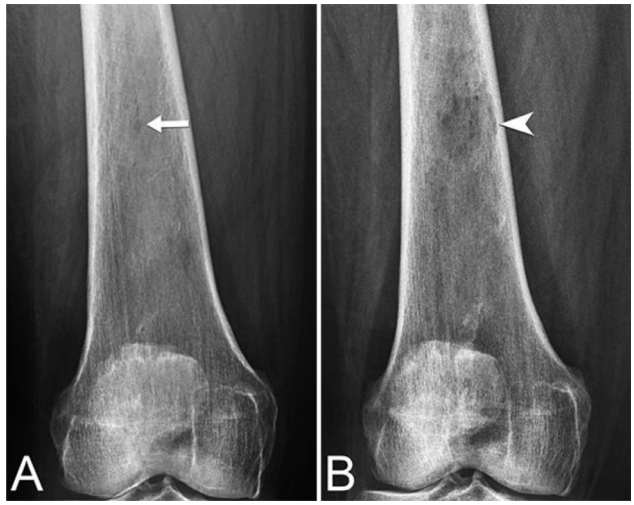

Figure 7 Sixty-nine-year-old female patient with progressive multiple myeloma. A barely perceptible lucency in the distal diaphysis of the femur (A, arrow), markedly enlarges 3 weeks later (B). The margins are ill-defined, indicating a highly aggressive lesion. Interval thinning of the cortex (arrowhead) increases fracture risk in this weight-bearing bone. Skeletal surveys are an inexpensive and readily available means of assessing risk for pathologic fracture. Because this survey only included AP images of the long bones, a lateral radiograph of the femur was requested to further assess fracture risk.

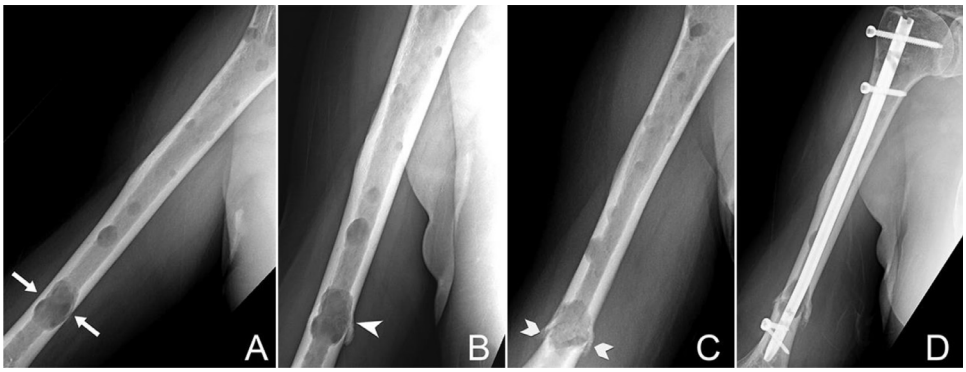

Figure 6 Sixty-six-year-old male with multiple myeloma in relapse following autologous stem cell transplantation. New baseline radiography of the right humerus (A) shows multiple well-defined lytic lesions. The largest, located in the distal diaphysis produces the greatest degree of cortical thinning (arrows). He received radiation therapy to this lesion 2 weeks later. Follow-up radiography obtained 3 months following radiation therapy (B) demonstrates an incomplete fracture through the lesion with callous at the medial cortex (arrowhead). The patient declined surgery. After another 3 months (C), the fracture has become complete and impacted (chevrons). Two weeks later (D), an intramedullary nail was placed, stabilizing the fracture and relieving pain.

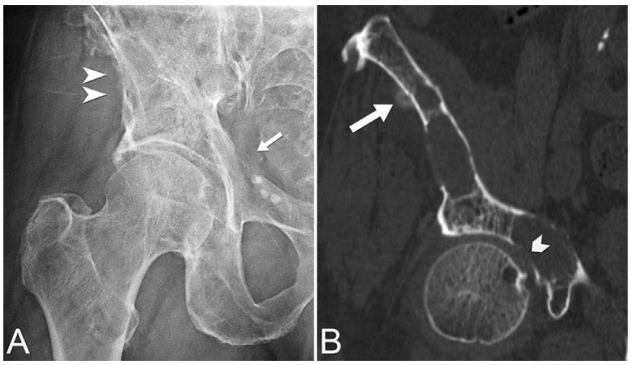

Figure 8 Same patient as in Figure 7. Radiography (A) demonstrates lysis of the pelvic ring opposite the medial right acetabulum (arrow) and another lytic lesion in the supra-acetabular iliac bone (arrowheads). Coronal CT reformation (B) reveals osteolysis of the articular surface of the medial acetabulum that was radiographically occult (chevron). The lesion in the supra-acetabular iliac bone demonstrates a pathologic fracture with callous much more clearly than on the radiograph (large arrow).

Low-dose protocols have been implemented to minimize radiation exposure while maintaining image quality.[28,29]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is typically used for the staging process in patients with MM, owing to higher sensitivity for lesion detection compared to skeletal surveys and other imaging techniques.[32-34] MRI permits optimal visualization of the bone marrow allowing the detection of marrow infiltration much earlier than the incidence of myeloma-related bone destruction. Whole-body MRI (WB-MRI) is preferred, if available, over conventional MRI of the spine and pelvis due to ability to detect extra-axial focal lesions[35] and lesions in the axial skeleton. Typically, myeloma lesions exhibit low signal intensity on T1-weighted (T1W) sequences, high signal intensity on T2-weighted (T2W) and short tau inversion recovery sequences, and contrast enhancement following intravenous gadolinium administration.[36,37] Numerous patterns of marrow involvement can be detected on MRI including normal pattern, focal involvement (focal lesions should be at least 5 mm in diameter), diffuse homogenous involvement, combined focal and diffuse involvement, and heterogeneous involvement. However, a normal marrow pattern on MRI does not completely rule out low-volume myeloma cell infiltration of the marrow. Heterogeneous marrow involvement demonstrates a heterogeneous salt-and-pepper appearance on MRI that may be due to the presence of normal fatty marrow mixed with small islands of myeloma cell infiltration, and is associated with a progressive course and unfavorable therapeutic response compared to other patterns.[38-41] Red marrow hyperplasia and stem cell transplant can also result in diffusely heterogeneous marrow. Bone marrow biopsy is the most accurate method of diagnosing an abnormal marrow pattern on MRI.

The appearance of myeloma on MRI correlates with the volume of tumor burden. High tumor burden is associated with diffuse hypointensity on T1W images and diffuse hyperintensity on T2W images, while low tumor burden is usually associated with normal pattern on MRI.[39] Furthermore, the marrow pattern on MRI has been linked to prognosis in patients with newly diagnosed MM. A high number of focal

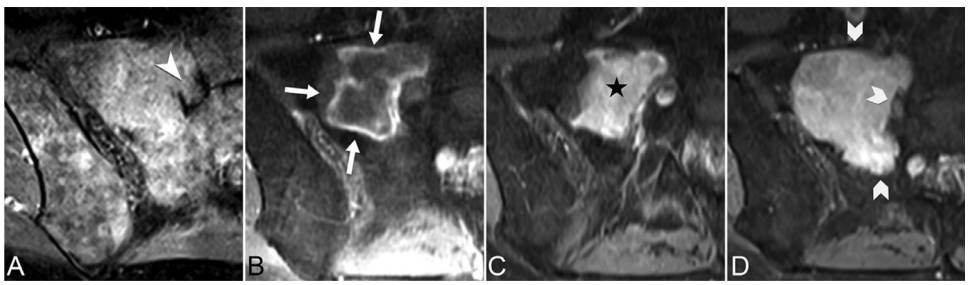

Figure 9 Sixty-nine-year-old female with multiple myeloma and a plasmacytoma. Pretherapeutic axial fat-saturated (FS) T1-weighted MRI following intravenous gadolinium contrast administration (A) demonstrates diffuse enhancement throughout the marrow cavity. The plasmacytoma in the right sacral ala enhances similarly to the marrow infiltration and is inconspicuous except for epidural tumor extending into the left S1 neural foramen (arrowhead). Diffuse tumor marrow infiltration or red marrow hypertrophy can be a pitfall on MRI, particularly in young patients with an abundance of normal red marrow (not shown). Post-therapeutic MRI following resolution of the marrow infiltration (B) provides clear delineation of the underlying plasmacytoma. The central enhancement within the tumor has also resolved, leaving a thin rim enhancement that commonly occurs in large plasmcytomas following successful therapy (arrows). One year later, the disease recurred and the plasmacytoma in the left sacral ala re-developed central enhancement (C, asterisk). There is no significant enlargement of this early recurrence, making it radiographically occult and also potentially difficult to discern on CT, but well visualized on MRI due to excellent soft tissue contrast resolution. Five months later (D), the lesion has enlarged with extension to the anterior cortex, increased epidural tumor contacting the right S1 nerve root and greater posterior extension (chevrons). An enlarging lesion should be easier to detect on other imaging modalities but most conspicuous on contrast-enhanced FS T1-weighted MRI.

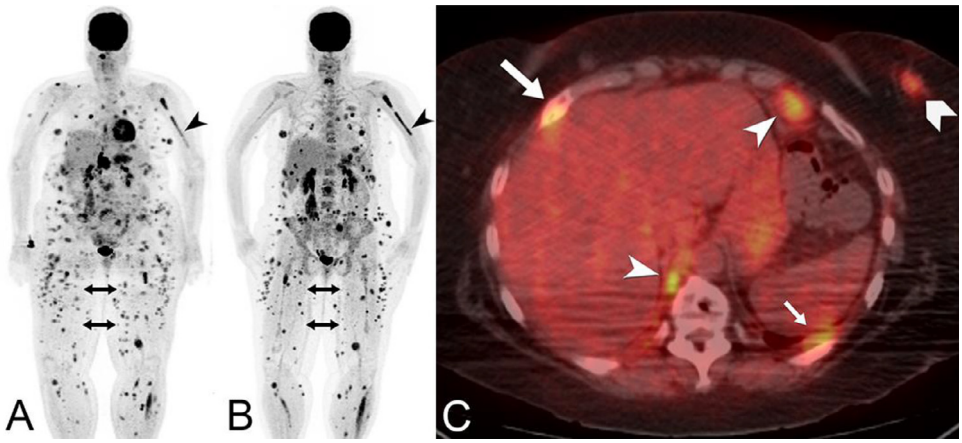

Figure 10 Forty-eight-year-old female with intramedullary and extramedullary myeloma. Whole-body maximum intensity projection FDG PET image (A) shows widespread FDG avid lesions in the skeleton, such as the left humerus (arrowhead) and in the soft tissues, particularly numerous in the thighs (double-headed arrows). One month following chemotherapy, there has been a mixed response to therapy (B). For example, the FDG uptake in the left distal humeral diaphysis has increased (arrowheads), while there has been a modest reduction in the overall number of soft tissue foci, such as in the medial thighs; soft tissue swelling has diminished following correction of acute renal failure (double headed-arrows). PET/CT can be an effective means of whole-body assessment. The cross-sectional nature of the scan (C) helps to localize the FDG avid lesions in bone (large arrow), pleura (small arrow) lymph nodes (arrowheads) and soft tissue (chevron).

lesions (>7 lesions) or presence of the diffuse pattern is associated with poor prognosis.[39,41,42] Additionally, MRI can be used to assess the response to therapy. With positive response to therapy, the marrow appearance on MRI slowly to the normal pattern,[26] unlike radiography. However, PET/CT can provide us with unique information regarding the metabolic response to therapy compared to MRI.[43] As the tumor cells die, they no longer take up the glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (FDG) and uptake diminishes. MRI has a few limitations including high cost, long scanning time which can represent a challenge in claustrophobic and terminally ill patients, exclusion of patients with some metallic devices, and personal variation of the MRI appearance of the disease, representing a possible challenge to determining the presence of marrow infiltration in some patients.[44] MRI can be useful in patients with suspected cord compression and to determine the need for interventional procedures such as vertebroplasty or kyphoplasty of compressed vertebral bodies or radiation therapy.[45] Moreover, it can help to differentiate between benign and malignant causes of vertebral fracture.[44]

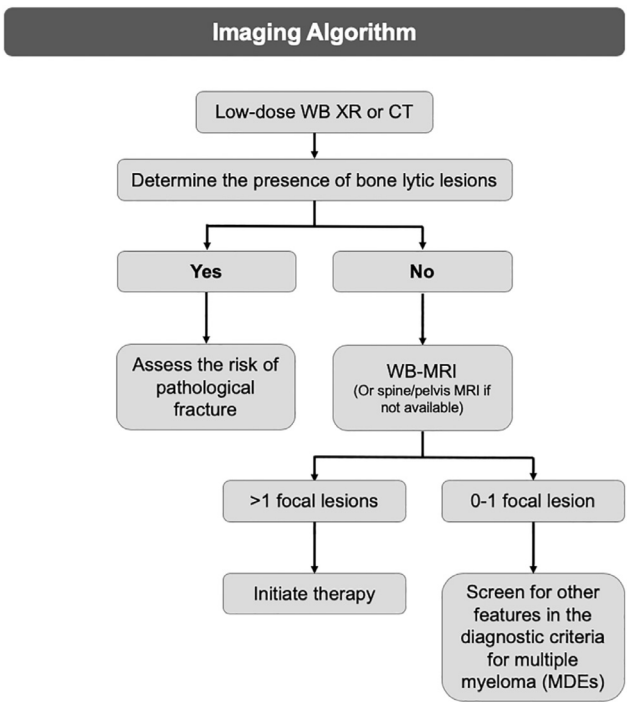

Figure 11 A step-wise algorithm for using different imaging modalities. WB-CT, whole-body CT; WB-XR, whole-body x-ray; WB-MRI, whole-body MRI; MDEs, myeloma defining events.

MRI plays an important role in predicting the risk of progression of SMM to symptomatic disease. The presence of more than 1 focal lesion on baseline WB-MRI is associated with an increased risk of progression with an approximate 2-year progression rate of 65%-70%.[46] Therefore, all patients with SMM should undergo WB-MRI, or spine/pelvic MRI if WB-MRI is not available. The presence of 2 of more focal lesions of at least 5 mm in diameter is the accepted indicator for presence of symptomatic disease that requires therapy initiation. In case of smaller/equivocal lesions, a follow-up MRI should be done within 3-6 months. In case of progression on MRI, therapy initiation should be considered[44] (Fig. 9). However, Merz et al found that the predictive value of demonstrating a progressive marrow pattern on serial WB-MRI is more accurate in estimating the risk of progression than the presence of focal lesions on baseline WB-MRI. Progressive patterns on WB-MRI include increased size of existing bone lesions, development of new focal lesions, and/or new bone marrow infiltration.[47]

Positron Emission Tomography/ Computed Tomography

FDG is the most commonly used tracer for PET imaging in MM and is a useful whole-body imaging modality for the assessment of myeloma patients (Fig. 10). FDG PET/CT helps to assess tumor burden and distinguish metabolically active from inactive lesions. FDG is taken up by metabolically hyperactive malignant plasma cells in place of glucose. PET scans are performed in conjugation with CT for attenuation correlation, and fused images allow accurate anatomical localization of the lesions. Compared to other imaging modalities, PET/CT has been found to be superior to WB-XR, while equally effective to MRI for detecting focal lesions. However, MRI is more sensitive for detecting bone marrow infiltration.[48,49] PET/CT is very beneficial after treatment and helps to distinguish radiologically apparent but metabolically inactive lesions from those resistant to treatment and are still metabolically active.[50,51] PET/CT can also help predict disease course and prognosis. Patients with higher standardized uptake values, which represents a quantitative measurement of FDG uptake and therefore the metabolic activity of a given lesion, demonstrate a more progressive disease course and worse prognosis compared to patients with low standardized uptake values values.[52,53] Additionally, complete suppression of abnormal activity on PET following treatment suggests a positive response to therapy and has been linked to better prognosis as compared to patients with incomplete suppression.[43]

Furthermore, Bartel et al found that the number of FDG-avid focal lytic bone lesions present after induction chemotherapy was linked to prognosis. The presence of 4 or more lesions was found to be associated with poor prognosis and inferior survival.[43] In general, PET/CT is considered the best imaging modality to evaluate the response to therapy by comparing the metabolic activity on post-treatment scans with pretreatment scans and also to identify patients with minimal residual disease.[54] Additionally, PET/CT provides a rough estimate for the risk of progression from SMM to symptomatic disease. Patients with SMM with metabolically active lesions on PET/CT scans are at a higher risk of progression to MM with an estimated 2-year progression of 75% compared to 30% in patients with negative PET/CT.[55]

PET/MRI is a novel, promising technique in patients with MM. The PET portion of the scan detects focal active lesions, while MRI determines their location and the degree of marrow involvement. This technique could be valuable in patients in biochemical remission, in order to help detect and localize residual disease activity and therefore guide treatment.[56] The use of different imaging modalities in patients with MM requires a stepwise approach (Fig. 11), which helps us to navigate our way during diagnosis, staging, prognosis, and therapy response in patients with MM.

Treatment

The details, guidelines, and different regimens for the treatment of MM are beyond the scope of this article. In general, the treatment of MM consists of combination chemotherapy to induce remission, followed by autologous stem cell transplantation for eligible patients.[57] In patients with asymptomatic MGUS or SMM, observation with regular follow-up is the standard of care. However, treatment should be considered in high-risk patients.[58]

Introduction of novel agents such as immunomodulatory drugs, for example, lenalidomide, and proteasome inhibitors, for example, bortezomib, combined with conventional chemotherapy can lead to dramatic improvement in prognosis and prolonged progression-free survival.[59] Furthermore, emergence of immunotherapy is showing promising results leading to improved prognosis and increased median survival.[60]

Conclusion

MM is the second most common hematologic malignancy. The malignant plasma cells infiltrate the normal bone marrow, and may invade the peripheral blood and other extramedullary organs causing end-organ damage. The IMWG has established an updated set of criteria for the diagnosis of MM and for differentiating it from other plasma cell disorders such as MGUS and SMM. Whole-body imaging modalities are considered part of the initial diagnostic work-up in patients with MM. Different imaging modalities, particularly MRI and PET/CT, play an important role in the staging process, risk stratification and prognosis prediction. Furthermore, they help to determine disease progression and can help evaluate the response to therapy. The use of imaging in MM is a stepwise strategy that starts with standard techniques like radiographic surveys, then progress to more advanced ones such as PET/CT and WB-MRI.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69:7-34, 2019.
2. Gonsalves W, Gertz MA, Gupta V, et al: Prognostic significance of quantifying circulating plasma cells in multiple myeloma. Clin Lymphoma Myeloma Leuk 14, 2014. S147-S
3. Kyle R, Child J, Anderson K, et al: 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
4. Kyle RA: Review of 1027 patients with newly diagnosed multiple myeloma. (Mayo Clinic Proceedings) (Author Abstract). JAMA 289:2047, 2003
5. Drayson M, Tang LX, Drew R, et al: Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. Blood 97:2900, 2001
6. VanValkenburg M, Pruitt G, Brill I, et al: Family history of hematologic malignancies and risk of multiple myeloma: Differences by race and clinical features. Cancer Causes Control 27:81-91, 2016
7. Landgren O, Gridley G, Turesson I, et al: Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. Blood 107:904, 2006
8. Riedel DA, Pottern LM: The epidemiology of multiple myeloma. Hematol Oncol Clin North Am 6:225-247, 1992

9. Kristinsson SY, Björkholm M, Goldin LR, et al: Patterns of hematologic malignancies and solid tumors among 37,838 first−degree relatives of 13,896 patients with multiple myeloma in Sweden. Int J Cancer 125:2147-2150, 2009
10. Fonseca R, Bergsagel PL, Drach J, et al: International Myeloma Working Group molecular classification of multiple myeloma: Spotlight review. Leukemia 23:2210-2221, 2009
11. Kyle RA, Remstein ED, Therneau TM, et al: Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 356:2582-2590, 2007
12. Rajkumar SV, Gupta V, Fonseca R, et al: Impact of primary molecular cytogenetic abnormalities and risk of progression in smoldering multiple myeloma. Leukemia 27:1738, 2013
13. Terpos E, Dimopoulos MA: Myeloma bone disease: Pathophysiology and management. Ann Oncol 16:1223-1231, 2005
14. Roodman GD: Mechanisms of bone lesions in multiple myeloma and lymphoma. Cancer 80(8 suppl):1557-1563, 1997
15. König C, Kleber M, Ihorst G, et al: Prevalence of iron overload vs iron deficiency in multiple myeloma: Resembling or different from MDS—and stem cell transplant (SCT)—patients? Clin Lymphoma Myeloma Leuk 13:671-680, 2013. e3
16. Dimopoulos MA, Kastritis E, Rosinol L, et al: Pathogenesis and treatment of renal failure in multiple myeloma. Leukemia 22:1485, 2008
17. Batuman V: The pathogenesis of acute kidney impairment in patients with multiple myeloma. Adv Chronic Kidney Dis 19:282-286, 2012
18. Rajkumar SV, Dimopoulos MA, Palumbo A, et al: International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15:e538-ee48, 2014
19. Brian GM, Durie Md DE. Salmon Md S. A clinical staging system for multiple myeloma correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 36:842-54, 1975.
20. Greipp PR, San Miguel J, Durie BGM, et al: International staging system for multiple myeloma. J Clin Oncol 23:3412-3420, 2005
21. Palumbo A, Avet-Loiseau H, Oliva S, et al: International staging system for multiple myeloma. J Clin Oncol 33:2863, 2015
22. Roodman GD: Pathogenesis of myeloma bone disease. Leukemia 23:435, 2008
23. 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. Nature Publishing Group, 1545, 2009
24. Giuliani N, Rizzoli V, Roodman GD: Multiple myeloma bone disease: Pathophysiology of osteoblast inhibition. Blood 108:3992-3996, 2006
25. Schmidt GP, Reiser MF, Baur-Melnyk A: Whole-body imaging of bone marrow. Semin Musculoskelet Radiol 13:120-133, 2009
26. Hanrahan CJ, Christensen CR, Crim JR: Current concepts in the evaluation of multiple myeloma with MR imaging and FDG PET/CT. Radiographics 30:127-142, 2010
27. Mulligan ME: Imaging Techniques Used in the Diagnosis, Staging, and Follow-Up of Patients With Myeloma. London, England: SAGE Publications, 716-724, 2005
28. Horger M, Claussen CD, Bross-Bach U, et al: Whole-body low-dose multidetector row-CT in the diagnosis of multiple myeloma: An alternative to conventional radiography. Eur J Radiol 54:289-297, 2005
29. Gleeson T, Moriarty J, Shortt C, et al: Accuracy of whole-body low-dose multidetector CT (WBLDCT) versus skeletal survey in the detection of myelomatous lesions, and correlation of disease distribution with whole-body MRI (WBMRI). Skelet Radiol 38:225-236, 2009
30. Kröpil P, Fenk R, Fritz L, et al: Comparison of whole-body 64-slice multidetector computed tomography and conventional radiography in staging of multiple myeloma. Eur Radiol 18:51-58, 2008
31. Terpos E, Kleber M, Engelhardt M, et al: European Myeloma Network Guidelines for the management of multiple myeloma-related complications. Haematologica 100:1254-1266, 2015
32. 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. Clin Imaging 30:440-441, 2006
33. Walker R, Barlogie B, Haessler J, et al: Magnetic resonance imaging in multiple myeloma: Diagnostic and clinical implications. J Clin Oncol 25:1121, 2007
34. Baur-Melnyk A, Buhmann S, Becker C, et al: Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. Am J Roentgenol 190:1097-1104, 2008
35. Bäuerle T, Hillengass J, Fechtner K, et al: Multiple myeloma and monoclonal gammopathy of undetermined significance: Importance of whole-body versus spinal MR imaging. Radiology 252:477, 2009
36. 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, 2009
37. Libshitz HI, Malthouse SR, Cunningham D, et al: Multiple myeloma: Appearance at MR imaging. Radiology 182:833-837, 1992
38. 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
39. 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
40. Dimopoulos MA, Moulopoulos LA, Datseris I, et al: Imaging of myeloma bone disease—Implications for staging, prognosis and follow-up. Acta Oncol 39:823-827, 2000
41. 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, 1998
42. 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
43. Bartel TB, Haessler J, Brown TLY, et al: F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 114:2068, 2009
44. Dimopoulos MA, Hillengass J, Usmani S, et al: Role of magnetic resonance imaging in the management of patients with multiple myeloma: A consensus statement. J Clin Oncol 33:657-664, 2015
45. Rajkumar SV, Kumar S: Multiple myeloma: Diagnosis and treatment. Mayo Clin Proc 91:101-119, 2016
46. Hillengass J, Fechtner K, Weber M-A, et al: Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 28:1606, 2010
47. Merz M, Hielscher T, Wagner B, et al: Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia 28:1902-1908, 2014
48. 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, 2007
49. Moreau P, Attal M, Karlin L, et al: Prospective evaluation of MRI and PET-CT at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial. Blood 124:2911-2918, 2014
50. Cholewinski IW, Castellon II, Raphael IB, et al: Value of precise localization of recurrent multiple myeloma with F-18 FDG PET/CT. Clin Nucl Med 34:1-3, 2009
51. Durie BGM, Waxman AD, D'Agnolo A, et al: Whole-body (18)F-FDG PET identifies high-risk myeloma. J Nucl Med 43:1457-1463, 2002
52. Zamagni E, Patriarca F, Nanni C, et al: Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood 118:5989-5995, 2011
53. Haznedar R, Akı SZ, Akdemir ÖU, et al: Value of 18F-fluorodeoxyglucose uptake in positron emission tomography/computed tomography in predicting survival in multiple myeloma. Eur J Nucl Med Mol Imaging 38:1046-1053, 2011

54. Cavo M, Terpos E, Nanni C, et al: Role of 18F-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 18:e206-ee17, 2017
55. Siontis B, Kumar S, Dispenzieri A, et al: Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: Identification of patients needing therapy. Blood Cancer J 5:e364, 2015
56. Fraioli F, Punwani S: Clinical and research applications of simultaneous positron emission tomography and MRI. Br J Radiol 87:20130464, 2014
57. Attal M, Harousseau J-L, Stoppa A-M, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 335:91-97, 1996
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, 2013
59. Palumbo A, Mina R: Management of older adults with multiple myeloma. Blood Rev 27:133-142, 2013
60. Kumar SK, Dispenzieri A, Lacy MQ, et al: Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. Leukemia 28:1122, 2013