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Comprehensive Updates in the Role of Imaging for Multiple Myeloma Management Based on Recent International Guidelines

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The diagnostic and treatment methods of multiple myeloma (MM) have been rapidly evolving owing to advances in imaging techniques and new therapeutic agents. Imaging has begun to play an important role in the management of MM, and international guidelines are frequently updated. Since the publication of 2015 International Myeloma Working Group (IMWG) criteria for the diagnosis of MM, whole-body magnetic resonance imaging (MRI) or low-dose whole-body computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography/CT have entered the mainstream as diagnostic and treatment response assessment tools. The 2019 IMWG guidelines also provide imaging recommendations for various clinical settings. Accordingly, radiologists have become a key component of MM management. In this review, we provide an overview of updates in the MM field with an emphasis on imaging modalities.

Keywords: *Multiple myeloma; Whole-body MRI; Low-dose whole-body CT; ^{18}F-FDG PET/CT; Diagnosis; Treatment response*

INTRODUCTION

Multiple myeloma (MM) is a hematological malignancy characterized by the ability of clonal plasma cells to proliferate in the bone marrow (BM). MM accounted for 1.8% of all malignancies and a little over 17% of hematologic malignancies in the United States in 2017 [1]. In recent years, the incidence of MM has continuously increased. In Korea, the crude incidence rate (number of new cases /100000 people) of MM was 1.0/100000 in 2000, but increased to 2.9/100000 in 2015 [2]. MM occurs mainly in elderly patients, with a median age of 69 years [3]. Hence, the incidence of MM is expected to increase as the global population ages.

Prior to advances in the understanding of its biology around a decade ago, MM was considered to have a morbid prognosis [4]. However, the evolution of treatment options, such as molecular targeted agents and immunomodulators, has led to improvements in the management of patients with MM (Fig. 1). With advances in new therapeutic and diagnostic tools that have dramatically changed the management of MM patients, the role of imaging has changed, resulting in frequent updates to the international guidelines for treating these cases. Most of the guidelines currently followed by clinicians are based on consensus reports from the International Myeloma Working Group (IMWG), founded in 2001, which has been changing the landscape of MM research. The National Comprehensive Cancer Network and the European Society for Medical Oncology have also recently updated their guidelines for MM, which emphasize the utility of imaging such as whole-

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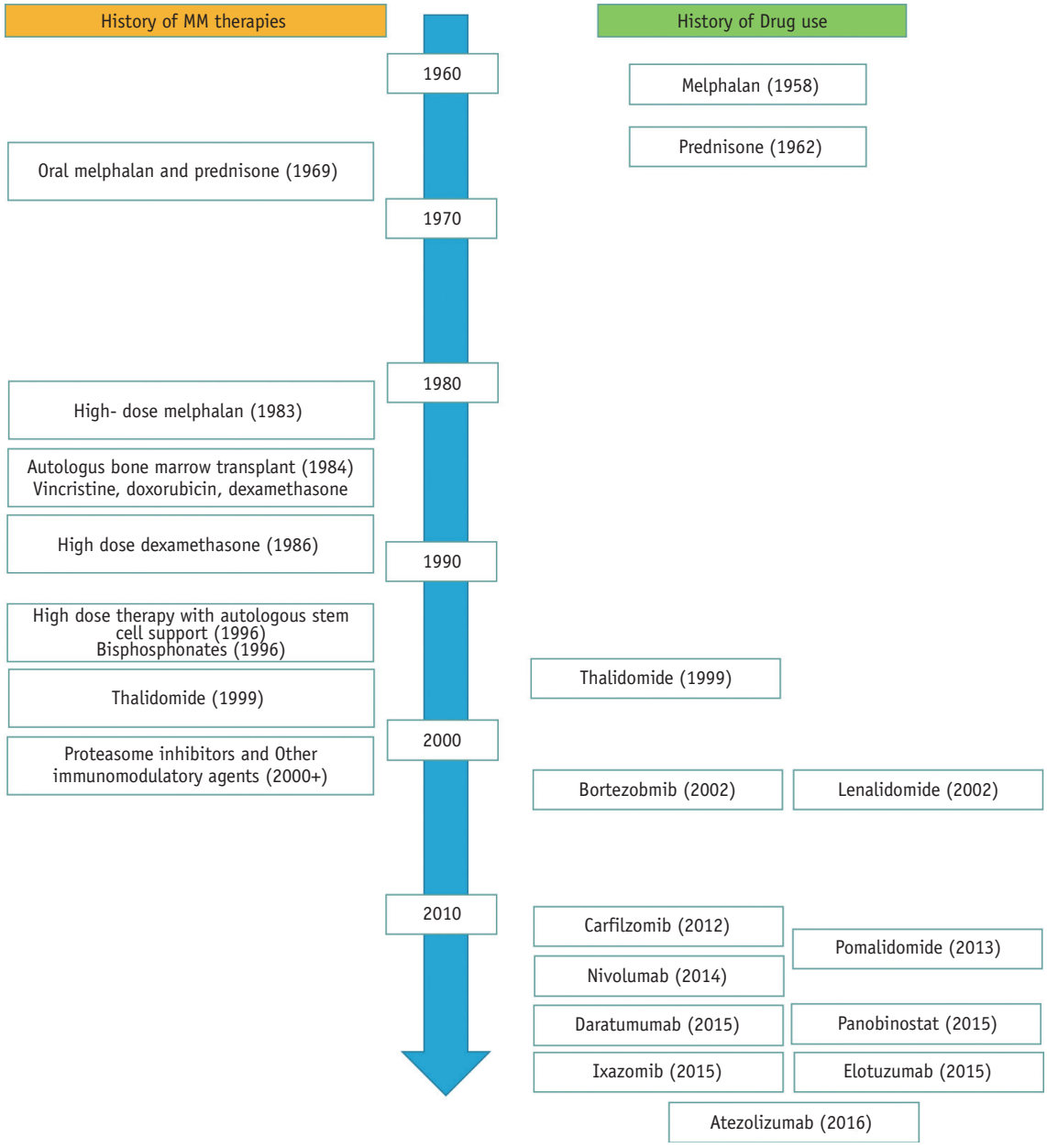

Fig. 1. History of MM drug development. The left part describes the development of MM therapies, and the right part describes the history of individual drugs approved for the treatment of MM. MM = multiple myeloma

body MRI (WBMRI) in the more recent versions [3].

The IMWG has announced several important guidelines for imaging utilization, as follows:

1) "Role of MRI in the management of patients with MM: A consensus statement" issued in 2015, which recommended the use of WBMRI as an important imaging method for detection and diagnosis of MM [5].

2) "Role of ^{18}F-fluorodeoxyglucose (FDG) PET/CT in the diagnosis and management of MM and other plasma cell disorders: A consensus statement by the IMWG" issued in 2017 recommended the use of ^{18}F-FDG PET/CT for initial disease evaluation and treatment response of MM [6].

3) "IMWG consensus recommendations on imaging in monoclonal plasma cell disorders" issued in 2019 suggested the optimal use of imaging methods at different disease stages in MM [7].

A multidisciplinary approach that includes imaging, clinicopathologic data, and genomic data for the optimized personalized care of patients with MM is ideal. The role of imaging techniques has increased in significance for the diagnosis, staging, and treatment monitoring of MM. Hence, radiologists should be aware of recent updates on

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the therapeutic and management guidelines of MM as key members of the multidisciplinary teams that treat these cases. In this article, we provide an overview of the current knowledge and guidelines in the field of MM, with a specific focus on imaging techniques.

Clinicopathologic Features

Plasma Cell Dyscrasia

Plasma cells, also referred to as plasma B cells and plasmacytes, are terminally differentiated B cells that produce antibodies (also called immunoglobulins or Igs). There are several types of plasma cell neoplasms that can cause confusion in a clinical setting. The following terminology delineates the separate entities that fall under the category of "plasma cell neoplasms" (Fig. 2) [8,9].

1) Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which myeloma protein (M protein), an abnormal antibody, is found in the blood. However, the level of serum M protein is < 3 g/dL and that of clonal BM plasma cells is below 10% in this disease [3]. MGUS does not cause any symptoms or major problems per se but can transform into MM at a rate of 1%/year, and regular monitoring is thus recommended [10]. MGUS is divided into three types: non-IgM MGUS, IgM MGUS, and light-chain MGUS.

2) Smoldering MM (SMM) is an asymptomatic clonal plasma cell disorder defined by the presence of a serum M protein level of ≥ 3 g/dL, or 10–60% clonal BM plasma cells without end-organ damage. SMM has a higher risk of progression to MM (5–10%/year) than MGUS does [10]. Currently, treatment for MGUS or SMM is not recommended, as these entities are regarded as premalignant [3].

3) MM is a cancer of plasma cells and clonal BM plasma cells. It is characterized by high levels of M protein and considerable end-organ damage, such as "CRAB" symptoms (increased calcium level, renal dysfunction, anemia, and destructive bone lesions).

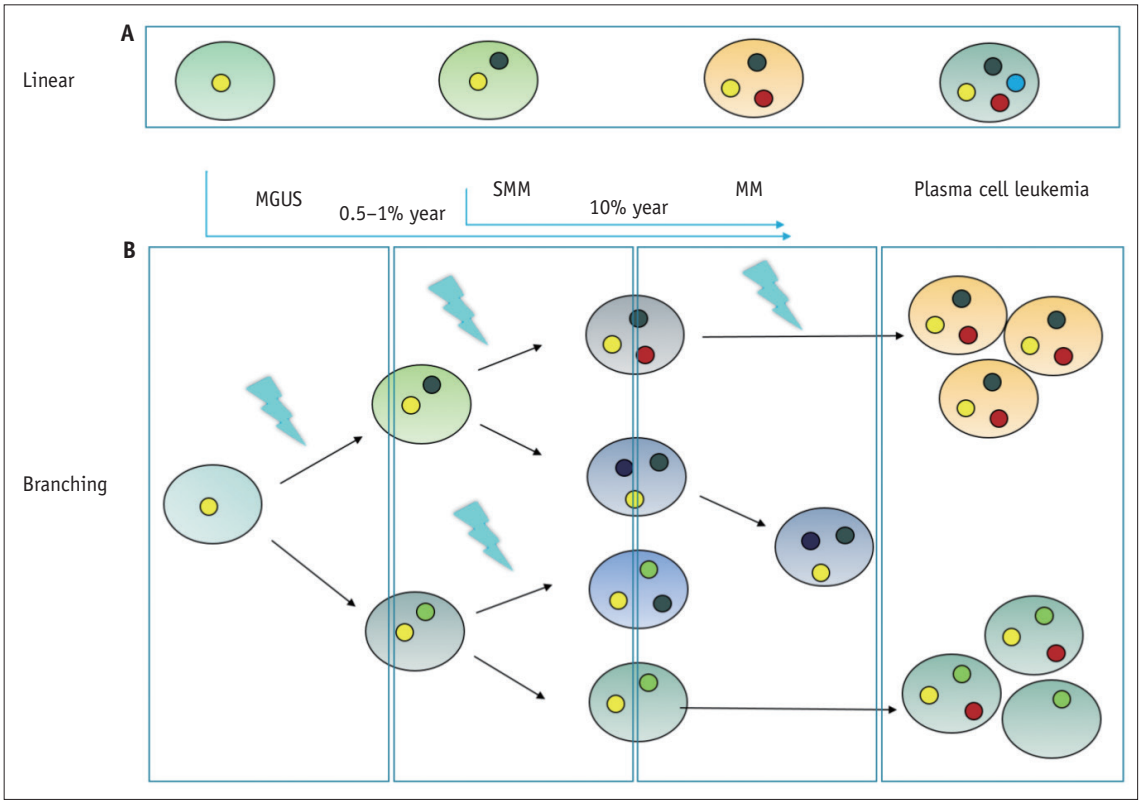

Fig. 2. Spectrum of plasma cell dyscrasia.
A. A previous model considered MM as being acquired through a multistep linear process of genetic hits causing a stepwise change of normal plasma cells from MGUS to SMM and MM. This is then followed by transformation into plasma cell leukemia. **B.** A recently developed model considers MM as a collection of tumor cells with a random acquisition of genetic hits and a Darwinian selection of the fittest clone which progresses in both a linear and branching manner, which accelerates clonal heterogeneity. This model of intra-clonal heterogeneity can explain the clinical features such as biclonal disease or class switch in relapsed patients with MM. MGUS = monoclonal gammopathy of undetermined significance, MM = multiple myeloma, SMM = smoldering MM

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4) Solitary plasmacytoma (SP) is a biopsy-confirmed solitary lesion of the bone or soft tissue, but not the BM, with concurrent normal or very low plasma cell infiltration in the BM (< 10%). Patients with SP show no signs or symptoms of end-organ damage and do not, therefore, manifest the CRAB symptoms seen in MM.

5) Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome is a paraneoplastic disorder that arises due to an underlying plasma cell neoplasm. It is defined by the presence of polyneuropathy and a monoclonal plasma cell-proliferative disorder with either Castleman disease, sclerotic bone lesions, or elevated vascular endothelial growth factor.

Signs and Symptoms

Most of the common signs and symptoms in MM can be explained by the abbreviation "CRAB." Also included in the diagnostic criteria for MM, CRAB stands for an increased calcium level, renal dysfunction, anemia, and destructive bone lesions (Table 1) [8]. Apart from a few cases that are diagnosed incidentally during the asymptomatic stage, MM is generally diagnosed in patients who present with symptomatic signs, such as bone pain or anemia. However, the clinical manifestations of MM are extremely diverse.

Anemia occurs in 70% of newly diagnosed MM cases. Patients may present with fatigue, muscle cramps, postural dizziness, and other symptoms. Bone pain, especially back pain, occurs in up to 58% of patients with MM, and lytic lesions are present in up to 80% of cases at diagnosis. Renal insufficiency is seen in 20–40% of newly diagnosed MM cases, but patients rarely present with dysuria or oliguria. Compared to other CRAB criteria, hypercalcemia is less common in MM, seen in up to 13% of patients. Hypercalcemia may present with symptoms such as confusion, muscle weakness, and constipation [11]. As there are no specific symptoms or signs for MM, a low index of suspicion in patients with CRAB symptoms should be used to initiate a full workup to diagnose this cancer, so that treatment is not delayed.

Table 1. Signs and Symptoms of Symptomatic Multiple Myeloma

Clinical Manifestation	Cause	Symptoms	When to Consider Myeloma
Anemia	Decrease in the number and activity of red blood cell producing cells	Fatigue Weakness	Vitamin B12, folate and iron studies normal No history of blood loss No hemolysis No clear alternative explanation such as renal impairment or anemia of chronic disease
High protein level	Release of abnormal or monoclonal proteins produced by the myeloma cells	Sluggish circulation Possible kidney damage	Usually requires that a diagnosis of multiple myeloma be confirmed. A small proportion of cases may be non-secretory with undetectable paraprotein
Bone damage (lytic lesions, fracture of vertebra)	The myeloma cells activate osteoclast cells and block osteoblast cells	Bone pain Bone welling Fracture or collapse of a bone	Evidence of bony lesions on imaging Crush fractures in a young patient Pathological fractures in unusual sites
High blood calcium	Release of calcium from damaged bone	Mental confusion Dehydration Constipation Fatigue Weakness	Parathyroid hormone appropriately suppressed Vitamin D normal No history of malignancy, sarcoidosis or use of medications such as thiazides
Reduced normal immune system function	Myeloma cells block production of normal antibodies against infection	Susceptible to infection Delayed recovery from infection	
Renal impairment			No clear explanation such as prerenal causes, primary renal disorders or obstructive conditions

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Diagnosis

In the past, a diagnosis of MM required the presence of end-organ damage, such as those defined by the CRAB criteria [5]. In 2015, the IMWG redefined the criteria for a diagnosis of MM by adding 'myeloma defining events'. This reflected a paradigm shift in clinical efforts to prevent end-organ damage and, as a result, improve the survival and quality of life in high-risk patients with SMM, rather than merely treating the symptoms that have already developed. This revision was based on the fact that SMM is biologically heterogeneous, with affected patients demonstrating a wide range of outcomes and progression rates to MM [12].

Accordingly, to diagnose high-risk patients at an early stage, a revised definition has added cases that do not meet the classic CRAB criteria so that the presence of at least one of the following markers is regarded as a case of MM (Table 2) [8]:

1) Clonal BM plasma cell percentage ≥ 60%

2) An involved/uninvolved serum free light chain ratio ≥ 100 with the involved serum free light chain ≥ 10 mg/dL (the involved chain refers to the abnormal monoclonal free light chain, while the uninvolved chain refers to the polyclonal immunoglobulin chain).

3) More than one focal lesion on MRI that is at least 5 mm in size.

These revised active MM criteria will not only increase the known prevalence of active MM but will also change the management guidelines and the ultimate clinical outcomes of the patients by facilitating earlier treatments. For an initial diagnostic workup for MM with history-taking and physical examination, IMWG recommends routine testing, such as complete blood counts with differentials, a chemistry panel including calcium and creatinine, serum protein electrophoresis, nephelometric quantitation of immunoglobulins, routine urinalysis, 24-hour urine collection for proteinuria, and quantification of both the urine M-component level and albuminuria [8].

As the bone disease is a principal feature of MM, bone imaging is essential for its diagnosis [13]. Extramedullary involvement is found in up to 10% of patients with MM

Table 2. New Definition of Active MM Released by the IMWG in 2015

Clonal bone marrow plasma cells > 10% or biopsy-proven bony/extramedullary plasmacytoma and any one or more of the following CRAB features and MDEs		
CRAB	Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder	- Hyper-Calcemia: serum calcium > 1 mg/dL higher than the upper limit of normal or > 11 mg/dL - Renal insufficiency: creatinine clearance < 40 mL/minute or serum creatinine > 2 mg/dL - Anemia: hemoglobin value of > 20 g/L below the lowest limit of normal, or a hemoglobin value < 100 g/L - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET/CT. If bone marrow has < 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
MDEs	Any one or more of the following biomarkers of malignancy	- Clonal plasma cells ≥ 60% on bone marrow examination - Serum involved/uninvolved free light chain ratio ≥ 100, provided the absolute level of the involved light chain is at least 100 mg/L - More than one focal lesion on MRI ≥ 5 mm
Initial image work-up: - Complete skeletal survey including spine, pelvis, skull, humeri and femurs - The IMWG now recommends the use of LDWBCT or MRI in the work-up of SMM and solitary plasmacytoma - The IMWG now recommends that one of PET/CT, LDWBCT, or MRI of the whole body or spine be done in all patients with suspected SMM, with the exact imaging modality determined by availability and resources - Clear evidence of one or more sites of osteolytic bone destruction (≥ 5 mm in size) seen on CT (including LDWBCT) or PET/CT fulfills the criteria for bone disease in MM, and should be regarded as meeting the CRAB requirements, irrespective of whether the lesions can be visualized on skeletal radiography or not - Increased uptake on PET/CT alone is not adequate for the diagnosis of MM; evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination - Bone densitometry studies are not sufficient to determine the presence of MM - The IMWG no longer recommends the presence of osteoporosis or vertebral compression fractures in the absence of lytic lesions as being sufficient evidence of bone disease for purposes of the diagnostic criteria		

IMWG = International Myeloma Working Group, LDWBCT = low-dose whole-body CT, MDE = myeloma-defining event, MM = multiple myeloma, SMM = smoldering MM

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at diagnosis, and commonly found sites include soft tissues surrounding the axial skeleton, lymph nodes, liver, kidney, airways, skin, and breast [14,15]. As the various bone imaging modalities have different characteristics and clinical utilities (Table 3), the IMWG established new guidelines in 2019 on the optimal use of various imaging methods, which are detailed below in a separate section.

Advances in the Treatment of MM

The complexity of MM management is such that assessments and treatment planning should be conducted in a stepwise and focused manner. Therapy should be initiated in patients with active or symptomatic MM. During the treatment workup process, it should also be decided whether the patient is eligible for autologous stem cell transplantation (ASCT). The treatment plans will need to differ in accordance with transplant eligibility. The first phase is induction therapy, which is the main treatment used to kill MM cells, with the goal of suppressing the disease as much as possible. In transplant-eligible patients, ASCT is performed, followed by consolidation therapy. Maintenance therapy should then be performed to prevent recurrence and stabilize the remaining tumor cells (Fig. 3) [16]. A notable recent change in the management of MM is that the line between transplant-ineligible and transplant-eligible patients has become less distinct [8,17]. Previously, most of the randomized studies for ASCT included patients younger than 65 years, and the decision on whether to conduct ASCT in patients older this age was controversial. However, survival outcomes in 'elderly' patients have improved since 2008 due to the development of novel treatment agents, and this has altered the concept that age should be considered when deciding on a combination of ASCT and novel-based regimens [8,17,18].

The role of maintenance therapy has been emphasized in recent MM treatment strategies [9]. In this maintenance approach aimed at stabilizing the remaining tumor cells, the

Table 3. Comparison of Imaging Modalities for Multiple Myeloma Evaluation

Modality	Pros	Cons
CSS	Low cost	Poor sensitivity/low detection rates
	Easy accessibility	Detection of only advanced osteolytic disease when at least 30–50% of the trabecular bone is destroyed
	Historic use/clinical validation	Long acquisition times
		No evaluation of bone marrow
		Poor differentiation of malignant vs osteoporotic vertebral fractures
		Cannot positively assess response
		Observer dependence
LDWBCT	Increased sensitivity for lytic disease	Radiation exposure
	3D information for biopsy, surgical or RT planning	Cannot positively assess treatment responses
	Detection of extramedullary plasmacytoma	Higher cost than CSS
	Rapid and comfortable scanning	Inability to assess for diffuse bone marrow infiltration disease or bone marrow lesions prior to bone destruction, especially in the cancellous bone of the spine and pelvis
	Less cost than PET/CT and WBMRI	
WBMRI	No radiation	Higher cost than CSS
	Depicts diffuse and focal myeloma	Long acquisition time
	Superior assessment of extramedullary disease and spinal cord compression	Patients with bone pain or an unstable status such as claustrophobia may not be able to endure the process
	Number of lesions is prognostic	Some patients are excluded due to metal implants
	Multiplanar information for biopsy, surgical or RT planning	Risk of nephrogenic systemic fibrosis when using contrast agent
PET/CT	Assess activity before and after treatment	Higher cost than CSS
	Extramedullary disease assessment	Long acquisition time
	CT component can define lytic diseases	Radiation exposure
	Novel information from alternate tracers	False-positive from inflammation
		Poor spatial resolution

CSS = complete skeletal survey, LDWBCT = low-dose whole-body CT, RT = radiation treatment, WBMRI = whole-body MRI, 3D = three-dimensional

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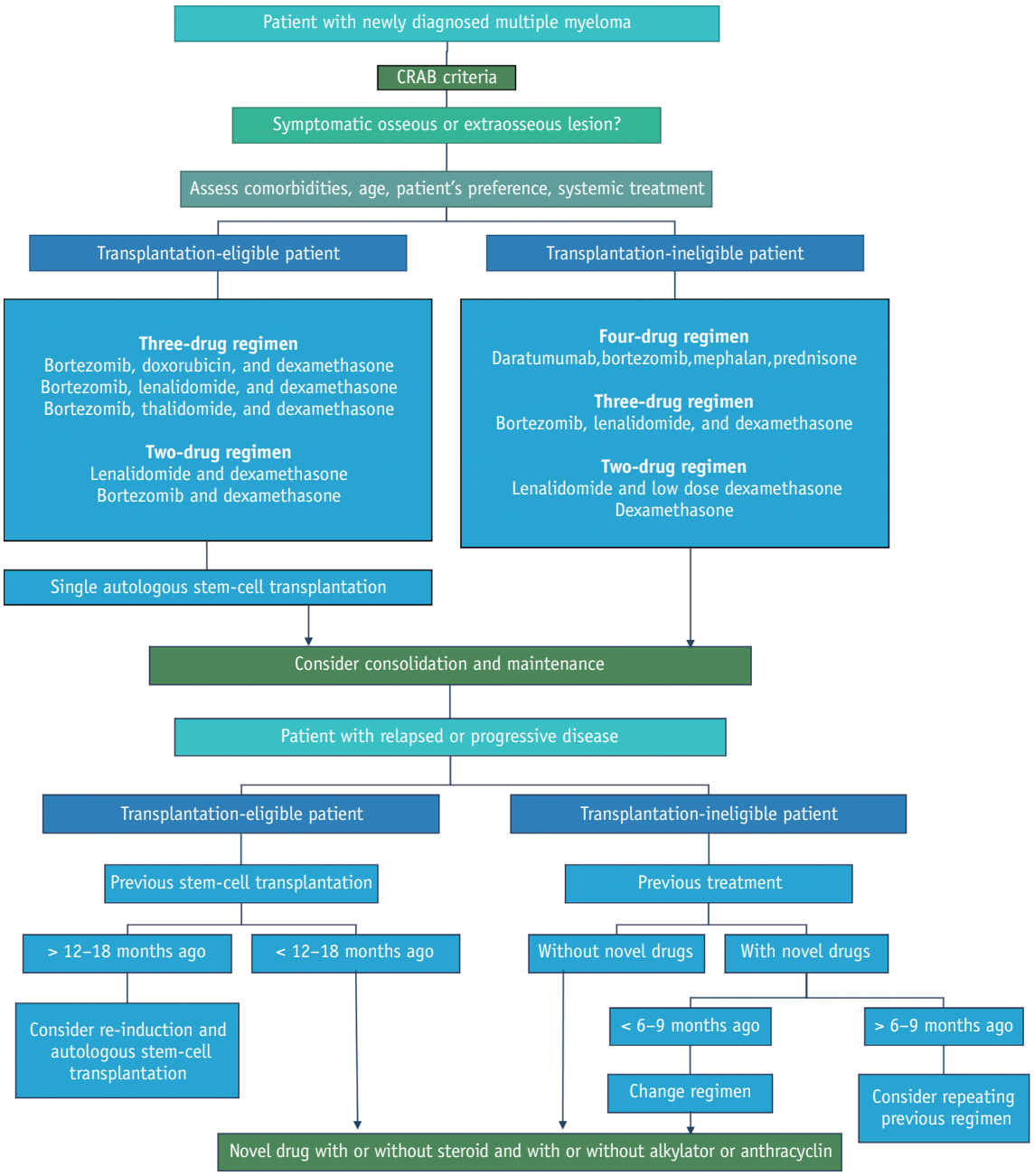

Fig. 3. Current treatment algorithm recommended for multiple myeloma (Based on International Myeloma Working Group and National Comprehensive Cancer Network guidelines). The algorithm summarizes the treatment regimens for patients with newly diagnosed multiple myeloma and patients with relapsed or progressive disease. These treatments differ mainly in accordance with the eligibility of the patient to receive stem cell transplantation.

newest drugs work through Darwinian selective pressure to modify the biology of the residual disease by selecting well-performing clones. Hence, the pressure must be adjusted to select the indolent clones. In short, stratifying the risk at an earlier stage in the disease course, and initiating treatment with a regimen of drug combinations followed by ASCT and intense maintenance therapy, is the currently favored treatment approach for MM (Fig. 3) [9].

In the past decade, and in tandem with new discoveries regarding the nature of MM, the development of novel drug regimens has changed the paradigm and outcomes with regard to symptomatic MM (Table 4) [19]. Bortezomib (Velcade®) was the first novel therapeutic agent for MM and was approved by the Food and Drug Administration (FDA) in 2003. Lenalidomide (Revlimid®), an immunomodulator, was approved by the FDA in 2006. Several other novel therapeutic

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Table 4. Currently Available Drugs for Multiple Myeloma by Pathway Category

Drug Class	Name (Brand)
Proteasome inhibitor	Ixazomib (Ninlaro), Carfilzomib (Kyprolis), Bortezomib (Velcade), Marizomib
Immunomodulator	Pomalidmide (Pomalyst), Lenalidomide (Revlimid)
Alkylating agents	Mephalan (Alkeran), Cyclophosphamide (Cytoxan)
Corticosteroids	Dexamethasone (Decadron), Predinisone (Deltasone)
Histone deacetylase Inhibitor	Panobinostat (Farydak), Vorinostat (Zolinza), Romidepsin (Istodax)
Bisphosphonates	Zoledronic acid (Zometa), Pamidronate (Aredia)
Monoclonal antibodies	Daratumumab (Darzalex), Elotuzumab (Empliciti), Silituximab (Sylvant), Cetuximab (Erbitux)
Immunotoxin	Indatuximab ravtansine
Hedgehog pathway inhibitor	BMS 833923
mTOR	Everolimus (Afinitor)
Akt inhibitor	Perifosine, Afuresertib
Aggresome/autophagy	Hydroxychloroquine
Kinesin spindle protein inhibitor	Filanesib
Cyclin-dependent kinase 4/6 inhibitor	Palbociclib
MEK1/2 inhibitor	Selumtinib (Koselugo)

MEK = mitogen-activated protein kinase, mTOR = mammalian target of rapamycin

drugs have since been approved, including carfilzomib (Kyprolis®) in 2012 and daratumumab (Darzalex®) in 2015, and have significantly improved the therapeutic outcomes for patients with MM. Histone-deacetylase inhibitors were introduced as a novel category of targeted drugs in 2014, and panobinostat (Farydak®) was the first agent to have been approved (Fig. 4) [8].

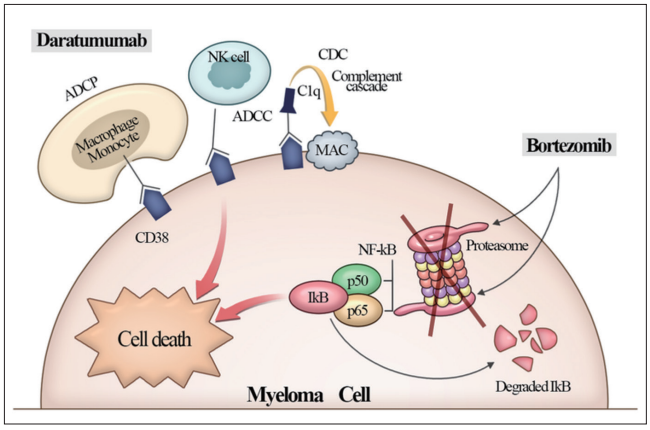

Fig. 4. Mechanisms underlying recent novel drugs for multiple myeloma. Daratumumab, an IgG1k monoclonal antibody, binds to CD38, leading to an apoptotic response in the cells through either antibody- or CDC. Bortezomib specifically and reversibly inhibits the threonine residue of the 26S proteasome, resulting in a loss of cell cycle and regulatory proteins and eventual cell death. ADCC = antibody dependent cell mediated cytotoxicity, ADCP = antibody dependent cellular phagocytosis, CDC = complement-dependent cytotoxicity, MAC = mitochondrial apoptosis-induced channel, NK = natural killer

The 2019 IMWG Recommendations on Imaging

The most recent IMWG consensus guidelines issued in 2019 emphasize the importance of using sensitive imaging methods to detect small or minimal disease and to assess the response accurately [7]. Hence, low-dose whole-body CT (LDWBCT), WBMRI, and ^{18}F-FDG PET/CT have become important imaging modalities for MM [20]. Furthermore, the 2019 IMWG guidelines recommend the optimal use of imaging methods at different disease stages in MM and for different purposes (Fig. 5). This is further discussed below.

Diagnosis and Staging

MM can be categorized into three stages using either the Durie-Salmon Staging System or the revised International Staging System (Table 5). Imaging plays an important role in the diagnosis and staging of MM [21]. In previous years, a skeletal survey using X-rays was the main imaging tool for the detection of lytic bone lesions in patients with MM. However, the IMWG now recommends whole-body FDG PET/CT, LDWBCT, or MRI of the whole body or spine, depending on the availability of each imaging modality in the clinical setting. As mentioned in the revised criteria for MM, a single osteolytic bone lesion ≥ 5 mm seen on CT (including LDWBCT) or on ^{18}F-FDG PET/CT is now regarded as meeting the CRAB criteria regardless of its visibility on skeletal radiography. However, an increased uptake on ^{18}F-FDG PET/CT requires evidence of underlying osteolytic bone lesions in the CT portion to be considered adequate for the diagnosis of MM. The IMWG recommends that a bone densitometry

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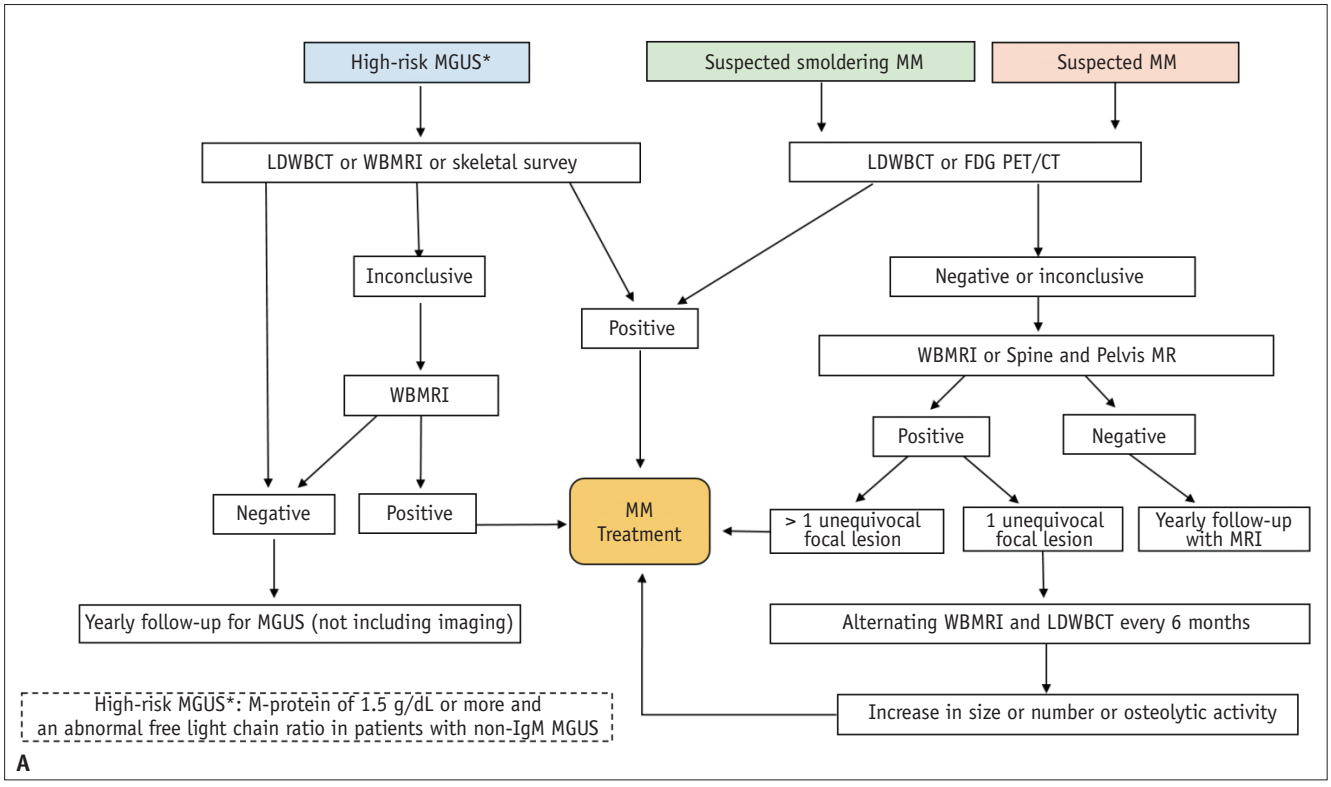

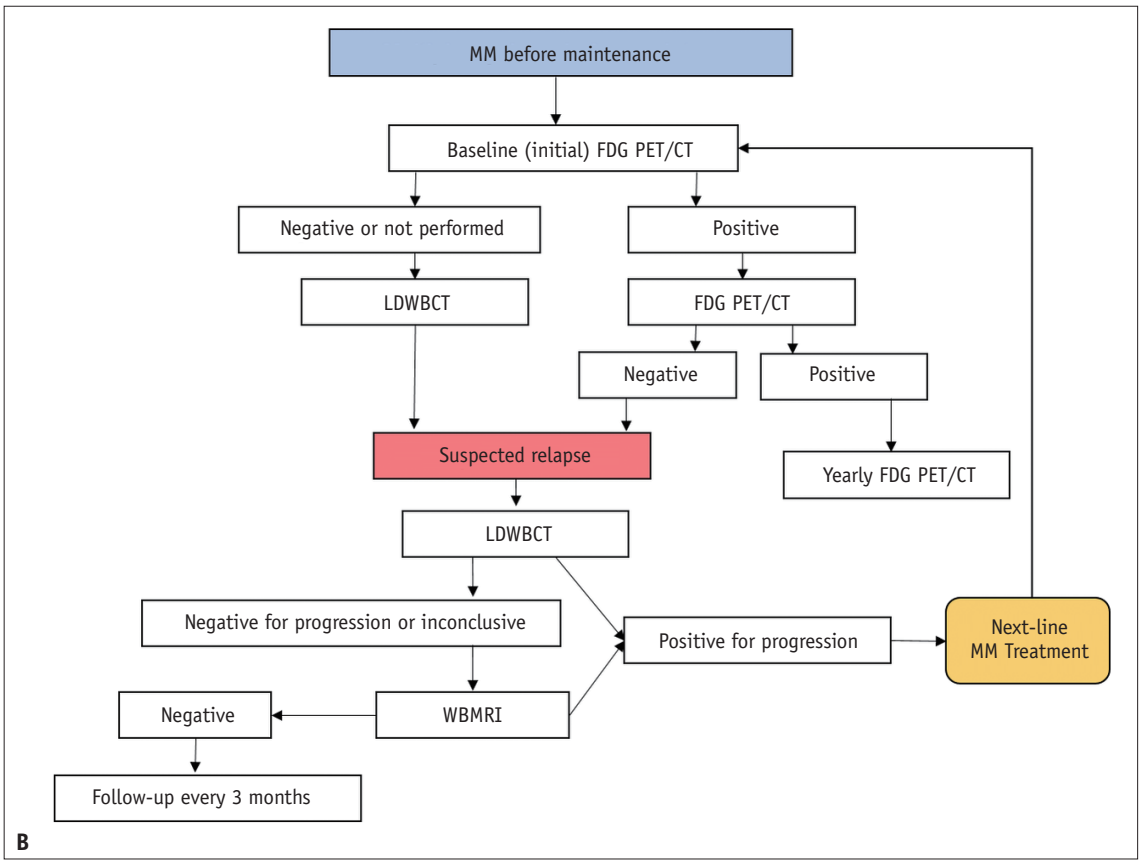

Fig. 5. 2019 International Myeloma Working Group recommendations for the imaging algorithm for MM.
A. Imaging algorithm for diagnosis and staging. **B.** Imaging algorithm for the treatment response. FDG = fluorodeoxyglucose, LDWBCT = low-dose whole-body CT, MGUS = monoclonal gammopathy of undetermined significance, MM = multiple myeloma, WBMRI = whole-body MRI

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Table 5. Multiple Myeloma Staging System

Stage	Durie-Salmon Staging System	R-ISS
I	• All of the followings: • Hemoglobin > 10 g/dL • Serum calcium ≤ 12 mg/dL • Absence of bone disease or solitary plasmacytoma • Serum paraprotein - IgG: < 5 g/dL, - IgA: < 3 g/dL • Urinary light chain excretion < 4 g/24 hours	• Serum beta2-microglobulin < 3.5 mg/L • Serum albumin ≥ 3.5 g/dL • Standard-risk chromosomal abnormalities • Normal lactate dehydrogenase
II	Not Durie-Salmon Stage I or III	Not R-ISS Stage I or III
III	• Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Skeletal survey with > 2 lytic lesions • Serum paraprotein - IgG: > 7 g/dL - IgA: > 5 g/dL • Urinary light chain excretion > 12 g/24 hours	• Serum beta2-microglobulin ≥ 5.5 mg/L • And one of the following 1) del (17p), t (4;14), and t (14;16) 2) High lactate dehydrogenase level

R-ISS = revised International Staging System

study is not adequate to diagnose MM. Moreover, the presence of osteoporosis or vertebral compression fractures without evidence of lytic bone lesions is also not sufficient for this diagnosis. This is because of the difficulty in detecting generalized osteoporosis using conventional X-rays, and because osteoporosis can be influenced by a variety of factors such as aging [5].

The 2019 IMWG consensus guidelines regarding the imaging algorithm for diagnosis and staging are illustrated in Figure 5A [7]. In patients with a suspected high-risk MGUS (i.e., M protein of 1.5 g/dL or more and an abnormal free light chain ratio in patients with non-IgM MGUS), LDWBCT is recommended as a first-line imaging test to rule out MM. If LDWBCT is not available, complete skeletal survey (CSS) or WBMRI are alternative modalities. In cases with negative imaging findings, a yearly laboratory follow-up is recommended. Follow-up bone imaging is not considered unless there are signs of progression to symptomatic disease. WBMRI was performed in cases with inconclusive findings on LDWBCT. In cases with positive imaging findings (i.e., focal and osteolytic lesions), active treatment for MM is initiated with a baseline FDG PET/CT.

In patients with suspected SMM or MM, LDWBCT is also the first imaging choice to exclude osteolytic lesions. If there are one or more osteolytic lesions, active treatment for MM is initiated with baseline FDG PET/CT. If the LDWBCT findings are negative or inconclusive, WBMRI is recommended to determine the presence of any focal bone lesions. ^{18}F-FDG PET/CT is an alternative to both LDWBCT and WBMRI. If negative findings are obtained for all of these imaging modalities, yearly imaging follow-ups should be repeated for at least 5 years, depending on the patient's risk factors. If a focal lesion is noted only on WBMRI, a subsequent LDWBCT should be considered checking for the possible development of osteolytic lesions. Active treatment for MM is considered if there are two or more unequivocal focal lesions on MRI because of the higher risk of progression [7].

Treatment Response Assessments

As novel therapies for MM have progressed in the last decade, appropriate response criteria have been emphasized alongside management guidelines. The IMWG issued criteria for clinical interventions in 2006 based on serum and urine M protein concentrations [22]. It revised these response criteria in 2016 by updating the concept of minimal residual disease (MRD) and by including imaging modalities, such as MRI and ^{18}F-FDG PET/CT for disease assessment and progression [22]. Notably, in 2017, the IMWG issued a new consensus statement that recommends ^{18}F-FDG PET/CT to evaluate and monitor the effects of therapy on myeloma-cell metabolism [6]. The inclusion of these imaging modalities has helped to determine the prognosis of suspected MM cases in many clinical settings [23].

According to the 2019 IMWG consensus guidelines on the imaging algorithm for MM treatment response assessments, ^{18}F-FDG PET/CT is the most sensitive tool for detecting

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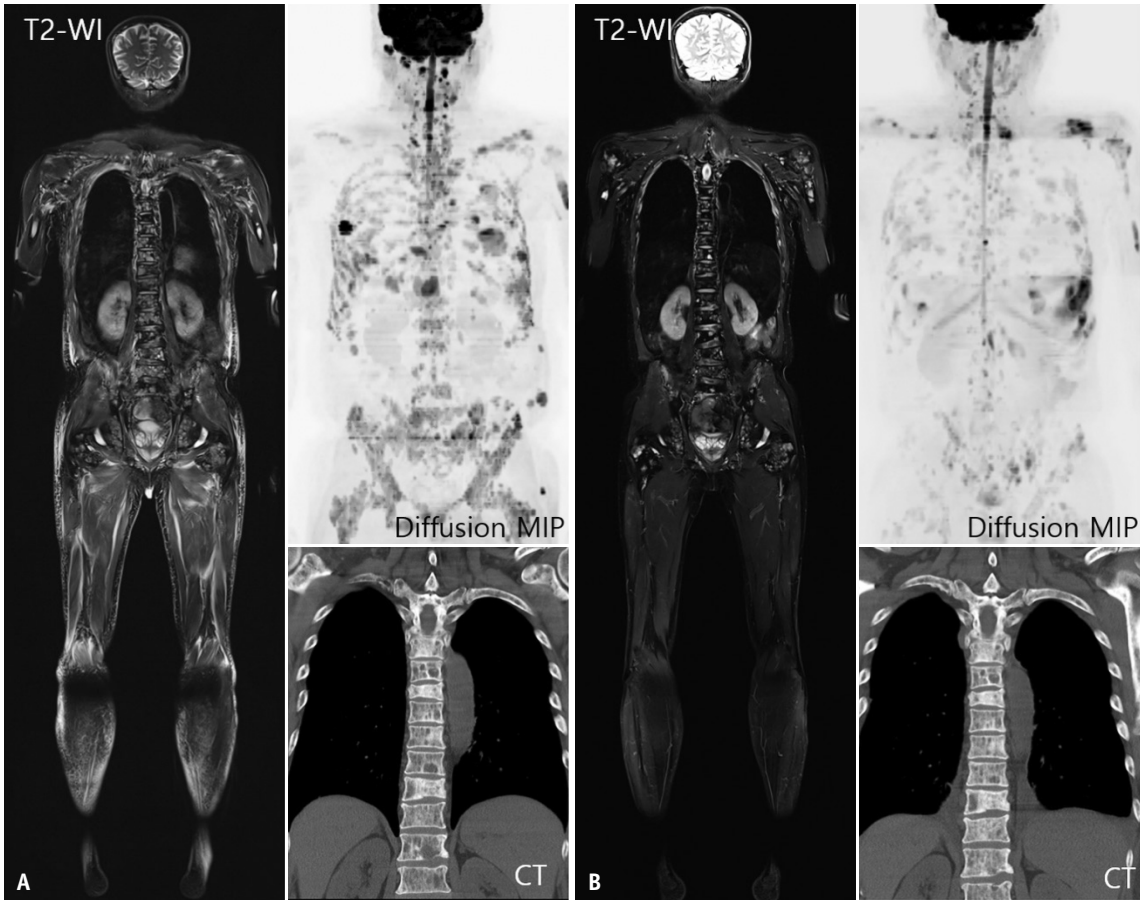

Fig. 6. A 52-year-old male patient with multiple myeloma treated with chemotherapy.
A. At the baseline WBMRI, numerous high signal intensity bone marrow lesions are evident on whole axial and appendicular skeletons on coronal T2-WI (left). These lesions showed diffusion restriction on a coronal diffusion MIP image (upper right). Multifocal osteolytic and osteosclerotic lesions were noted at the thoracic spine on a coronal CT (lower right). **B.** On the coronal T2-WI and diffusion MIP images taken 2 months after chemotherapy initiation, a marked decrease in bone marrow lesions is noted (left, upper right). Despite the huge changes evident on a follow-up MRI, only minimal effects on the osteolytic and osteosclerotic lesions were noted on a coronal chest CT (lower right). MIP = maximum intensity projection, WI = weighted imaging, WBMRI = whole-body MRI

decreased tumor viability during treatment as well as MRD, as long as there are FDG-avid lesions (Fig. 5B). Hence, baseline FDG PET/CT is recommended before starting chemotherapy in patients with MM [7]. If there is no FDG-avid lesion (negative finding), then the same imaging technique used at the initial diagnosis (either LDWDCT or WBMRI) should be used for the treatment response assessment. If there are residual FDG-avid lesions, yearly ^{18}F-FDG PET/CT is recommended until a complete metabolic response is achieved, after which it is only recommended again if relapse is suspected.

In MM cases with suspected relapse, LDWBCT is performed to evaluate the bone lesion status in comparison with prior results with this modality. If there are signs of progression on LDWBCT, the next line of active treatment for MM is newly commenced in conjunction with a baseline ^{18}F-FDG PET/CT. WBMRI is performed if there are negative or inconclusive findings on LDWBCT. The next line of active treatment is considered if these WBMRI findings indicate further signs of progression [7].

Recent Advances in Imaging Modalities

X-Ray and CT

CSS utilizes X-rays to scan the skull, chest, spine, pelvis, humeri, and femora [24]. This is a relatively simple method that is readily available worldwide. However, CSS has limited sensitivity for detecting osteolytic bone lesions compared to CT. Previous studies have found that lytic lesions are only detected by CSS when at least 50% of the bone is destroyed [25]. In contrast, LDWBCT can detect bone lesions at a 5% level of trabecular bone destruction

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and is therefore significantly superior to CSS [24]. Moreover, a prior systematic review reported that, compared to CSS, CT has up to a 33% higher detection rate for bones [24]. In a further multicenter study, the IMWG reported that LDWBCT gave a positive diagnosis in 25.5% of patients who had negative CSS results [26]. Hence, the 2019 IMWG consensus guidelines recommend replacing CSS with LDWBCT whenever possible [7].

Owing to the high-contrast nature of bone, the radiation dose required for CT bone evaluation can be lower than that used in CT acquisitions for soft tissue diseases. LDWBCT radiation doses as low as 3.2–4.8 mSv have been reported to yield an accurate diagnosis while preserving image quality [27]. LDWBCT is therefore the modality of choice in many institutions at present for the assessment of lytic bone lesions and fracture risk in patients with MM [28].

MRI

WBMRI technology has undergone significant recent advances enabling high-quality anatomical and diffusion-weighted imaging (DWI) in just 30–60 minutes. This, in turn, has led to the increased use of WBMRI in clinical practice. Currently, MRI is considered the most sensitive imaging modality for assessing the patterns and severity of BM infiltration in patients with MM without radiation exposure. This modality shows a positive predictive value of 88.7% for BM infiltration, even in the early stages of MM [29]. MRI is mandatory in cases of suspected spinal cord compression [30] and, even without the presence of bone destruction, can detect early BM involvement. Thus, MRI has a higher sensitivity than WBLDCT for detecting viable tumors in osteolytic bone disease (Fig. 6).

The IMWG guidelines released in 2015 recommended WBMRI as a first-line imaging modality, defining the presence of more than one focal lesion ≥ 5 mm in size as a diagnostic criterion for MM that warrants the initiation of therapy [8]. The 2015 IMWG guidelines aimed to identify high-risk SMM patients who might progress to MM within 2 years. Of note, recent studies have reported that MRI has prognostic value in MM, particularly in the first images taken at diagnosis [5,31,32]. In patients with SMM with indeterminate or equivocal focal lesions on WBMRI, the 2015 IMWG guidelines recommend a repeat MRI exam after 3 to 6 months [12].

Bone lesions in MM are typically hypo-intense in T1-weighted images and hyperintense in fat-suppressed T2-weighted images. This is due to a low fat content, high cellularity, and high water content in the lesions. Lesions

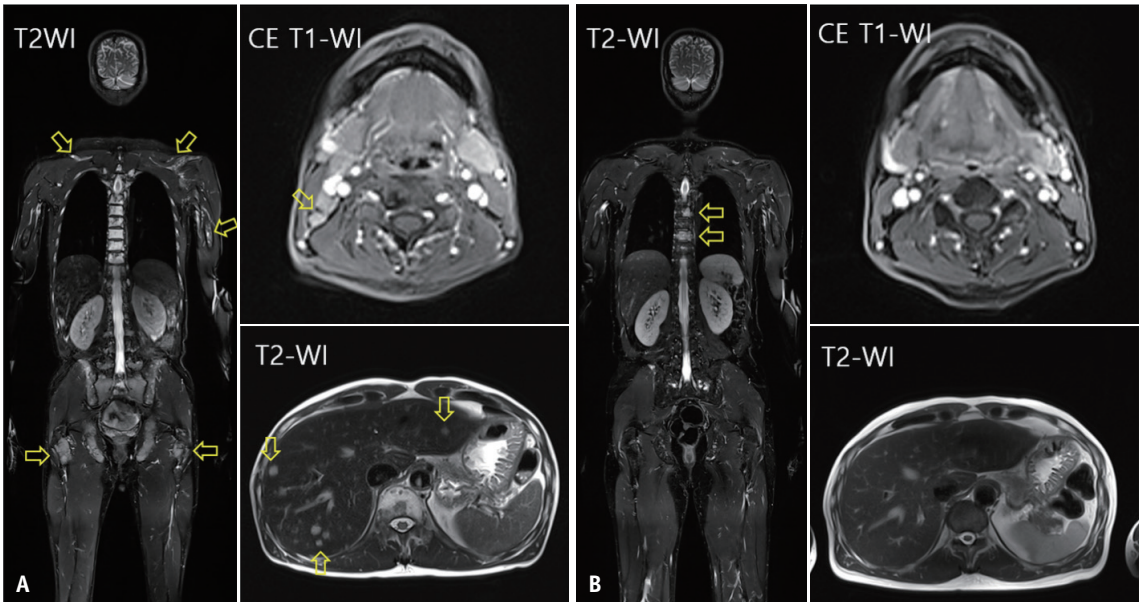

Fig. 7. A 55-year-old male patient with MM treated with chemotherapy and showing a discrepancy between the clinical and imaging response.
A. A coronal T2-WI image shows diffuse bone marrow high signal intensity at the whole spine, pelvis, left humerus, bilateral femur, and scapula (left, arrows). An axial CE T1-WI shows two enlarged lymph nodes at the right neck level II (upper right, arrow). An axial T2-WI indicates multiple high signal intensity nodules at the bilateral hemi livers, suggestive of extramedullary myeloma involvement (lower right, arrows).
B. Despite the clinical complete response, persistent bone marrow high signal intensity lesions are evident at the T6 and T8 vertebral body on a coronal T2-WI (left, arrows). Axial CE T1-WI and axial T2-WI images indicate the complete resolution of the extramedullary involvement of the MM in the lymph nodes and liver (upper, lower right). CE = contrast-enhanced, MM = multiple myeloma, WI = weighted imaging

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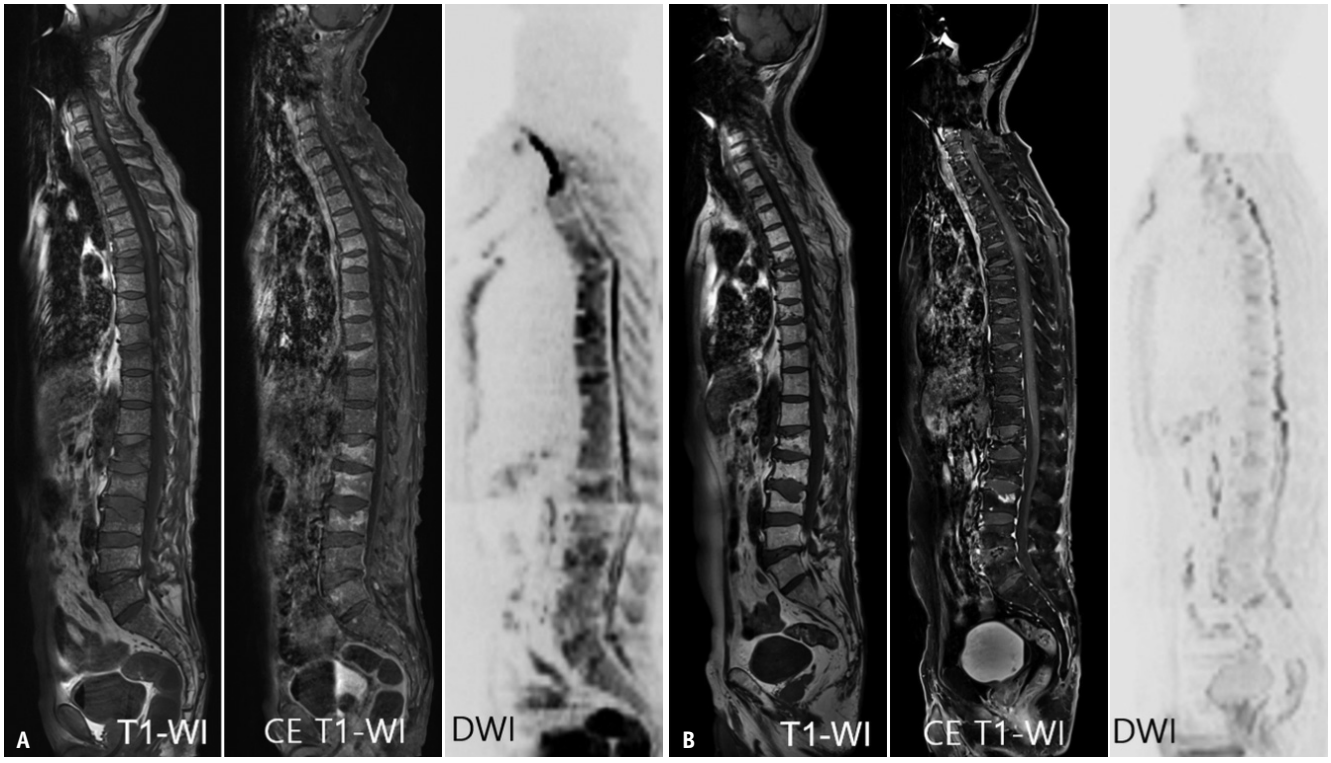

Fig. 8. A 66-year-old male patient with multiple myeloma treated with chemotherapy and showing a complete response on WBMRI.

A. At the baseline WBMRI, disseminated bone marrow lesions are noted along the whole spine with low signal intensity on T1-WI (left), enhancement on CE T1-WI (middle), and high signal intensity on DWI (right). **B.** On the T1-WI taken 1 year after chemotherapy initiation, all bone marrow lesions have disappeared (left). No enhancement or high signal intensity is noted on a CE T1-WI (middle) or DWI (right). CE = contrast-enhanced, DWI = diffusion-weighted imaging, WI = weighted imaging, WBMRI = whole-body MRI

scanned prior to therapy can appear as a nonspecific diffuse contrast enhancement and need to be differentiated from other infiltrative processes, such as lymphoma or metastasis. The first study to describe MRI findings of MM has reported four patterns of BM infiltration as focal, diffuse, variegated, and normal patterns with its possible value as a prognostic indicator [33]. They have recently been classified into five distinct patterns: normal appearance, focal lesions, diffuse infiltration, combined focal and diffuse infiltration, and a mixed micronodular or variegated salt-and-pepper pattern [34].

In recent studies, a BM infiltration pattern and the number of focal lesions were shown to be prognostic factors in MM. More than seven focal lesions in symptomatic patients with MM had prognostic significance, and more than one focal lesion was related to a poor prognosis in the early stages of MM [5]. More than one lesion on MRI was also found to be related to the progression of MGUS and SMM to MM when the time to progression was measured. The salt-and-pepper pattern was associated with stage I disease, while focal lesions and diffuse infiltration patterns were associated with stage II or III MM. In addition, patients with diffuse infiltration patterns have an increased risk of progression [5]. The IMWG does suggest that extra attention be paid to patients with a diffuse pattern, as it may signify a higher risk of progression to MM and an adverse outcome [24]. Currently, studies regarding the use of WBMRI are heterogeneous, and there is a lack of multicenter studies. Further studies that incorporate different clinical settings across a range of institutions are warranted to investigate the impact of advanced techniques, different MRI sequences, protocol standardization, and cost-effectiveness management (Fig. 7) [15].

DWI is a functional MRI technique that uses the self-diffusion of water molecules within tissues to determine the signal intensity. Based on this phenomenon, the apparent diffusion coefficient (ADC) is the most frequently used diffusion-related quantitative biomarker [12]. The microstructure of the tissue in question influences the ADC, and the particular structure of the BM cellularity causes unique paradoxical diffusion effects compared to other tissues [29]. For example, a BM infiltrated by tumor cells

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has a higher ADC than a normal BM [35].

As mentioned earlier, conventional MRI has limitations in evaluating the response to treatment in MM cases, and this can potentially be overcome by a functional technique such as DWI, which can detect treatment-induced changes in cellularity (Fig. 8) [12]. In general, active myeloma marrow shows a significantly higher ADC value than that of myeloma marrow in remission. However, changes in ADC values may differ depending on the timing of measurement due to marrow fat. For example, a study reported that ADC values were decreased at 4–6 weeks but increased at the 20th week of treatment in the good response group [36]. The ADC response pattern may vary among the BM infiltration patterns of MM [37]. For example, a study reported that ADC values in patients with focal lesions were increased in the good treatment response group, but no significant ADC changes were found in patients with diffuse and salt-and-pepper patterns [38].

DWI is useful for non-invasive longitudinal monitoring of the treatment response and can be complementary to laboratory methods [29]. Currently, treatment response assessment in patients with MM is performed by measuring M protein levels in blood and urine samples. However, M protein measurement may be hampered due to false-negative potential in oligosecretory/non-secretory MM and false-positive potential in the use of targeted antibody therapies, such as daratumumab, which may falsely increase M protein after treatment [39,40]. A limitation of DWI is that it is sensitive but not specific for an MM diagnosis, and DWI parameters usually change late in disease evolution. Whole-body DWI is under investigation as a modality for diagnosing MM [30].

Dynamic contrast-enhanced (DCE) MRI is another novel MRI sequencing technique that uses contrast gadolinium and measures T1 changes in tissues over time. This method aims to evaluate and quantify the time course of the contrast enhancement. Due to its small molecular size (500–1000 Da), gadolinium can reach the extracellular space by passing the vascular endothelium via passive diffusion, except in the brain and spinal cord. DCE-MRI can provide additional information including tissue vascularization, capillary permeability, and the volume of

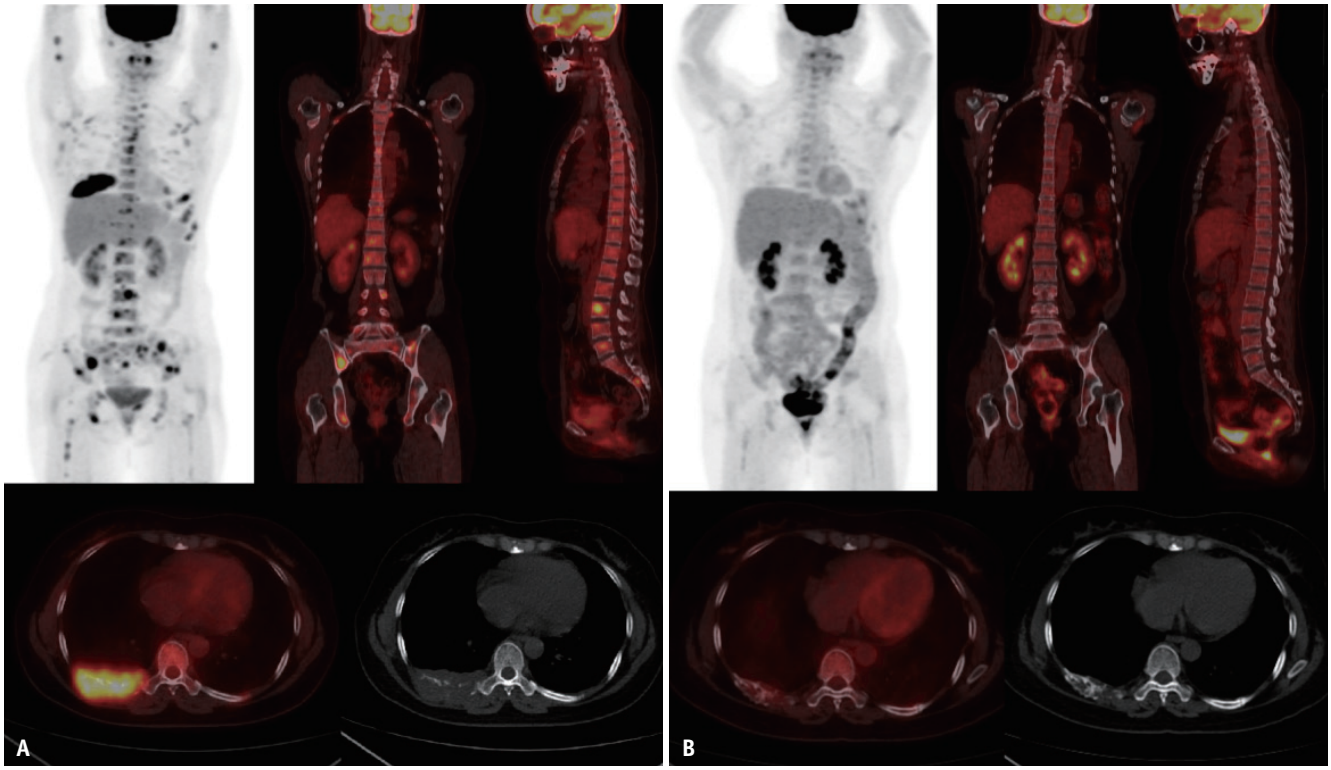

Fig. 9. A 58-year-old female patient with multiple myeloma treated with chemotherapy and showing a response by ^{18}F-FDG PET/CT.

A. At the baseline ^{18}F-FDG PET/CT, numerous hypermetabolic lesions are evident showing focal increased bone marrow uptakes in the whole axial and appendicular skeleton with several lesions showing extramedullary extension to soft tissue. **B.** The ^{18}F-FDG PET/CT taken 2 months after chemotherapy initiation shows almost a complete disappearance of focal hypermetabolic lesions in the whole-body skeleton with mild hypermetabolic activities and new bone formation in the previous osteolytic rib lesion. FDG = fluorodeoxyglucose

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the interstitial space.

MM is a hematological malignancy that demonstrates the importance of angiogenesis in disease development and prognosis. Angiogenic and anti-angiogenic molecules mediate the interaction between plasma cells and the BM microenvironment [12]. DCE-MRI allows for the evaluation of the microcirculation of the whole BM. Hillengass et al. reported an increase in spinal angiogenesis on DCE-MRI, which provides additional information on the disease activity and MM prognosis [41]. The combination of anatomical information provided by conventional MRI with these advanced techniques may prove useful. Indeed, Dutoit et al. reported that DCE-MRI and DWI were helpful in monitoring responses to therapy in patients with MM, especially after stem cell transplantation [23,41].

FDG PET/CT

In FDG PET/CT imaging, lesion uptake is suggestive of active myeloma, which reflects the metabolism of myeloma cells. Compared to CSS, ^{18}F-FDG PET/CT has the advantage of detecting intramedullary and extramedullary disease involvement in the whole body [6]. The use of whole-body ^{18}F-FDG PET/CT in the evaluation and monitoring of myeloma treatment responses has gained increasing acceptance, and a new consensus statement was issued in this regard from the IMWG in 2017 [6]. Based on this consensus statement, a combination of FDG PET and morphological testing, such as CT or MRI, enables MM detection in its early phase. Moreover, this approach can be used for both intramedullary and extramedullary MM to define the disease location, size, extent, and metabolic activity, and to monitor the treatment response by differentiating metabolically active from inactive sites. The 2017 consensus statement regards FDG PET/CT as the gold standard for evaluating and monitoring the MM treatment response (Fig. 9).

Evaluation of residual tumors is crucial for the further management of patients with MM after initial treatment [6]. The distinct advantages of FDG PET/CT are that it can differentiate highly cellular tissue from necrotic tissue, thus allowing residual disease assessment after therapy [42]. ^{18}F-FDG PET/CT can detect early metabolic changes, while the appearance of treatment response is usually delayed on MRI because of the slow changes in marrow signal abnormalities [22]. ^{18}F-FDG PET/CT is particularly helpful if the tumor burden is low, which is often the case after systemic therapy [6]. In terms of the predictive and prognostic value of ^{18}F-FDG PET/CT, the presence of focal lesions on ^{18}F-FDG PET/CT in newly diagnosed transplant-eligible patients with MM is an established independent prognostic indicator of both overall survival and progression-free survival [30]. In addition, a negative ^{18}F-FDG PET/CT was found to be related to a better prognosis in post-ASCT patients.

The limitations of ^{18}F-FDG PET/CT imaging must also be considered. In the first instance, there are several types of benign lesions that can show false-positive results with this method. These include infections, postsurgical changes, fractures, and some benign bone lesions. False-negative results may also occur with ^{18}F-FDG PET/CT imaging under certain conditions, such as high-dose steroid usage by the patient or hyperglycemia. In addition, ^{18}F-FDG PET/CT has a low sensitivity for detecting diffuse BM infiltration and may fail to detect small osteolytic lesions that are < 10 mm [43]. Another important limitation of ^{18}F-FDG PET/CT was demonstrated in a recent study of patients who underwent therapies that included a proteasome inhibitor. No significant association was noted between the clinical response and FDG findings of residual disease detection. In addition, ^{18}F-FDG PET/CT may not be the optimal choice for evaluating the treatment effects of targeted immune drugs [20]. Finally, one of the central limitations of ^{18}F-FDG PET/CT is that it has an unclear definition of PET positivity, which is currently defined by visual criteria that can be biased by inter-observer error [30]. The lack of parameter standardization has an impact on data reproducibility and interpretations of the patient response after therapy, warranting the need for consensus criteria [20].

CONCLUSION

Recent updates in the IMWG guidelines for the diagnosis and management of MM have revealed the importance of imaging in this hematologic malignancy. MRI is now crucial for the initial diagnosis of patients with active MM, and ^{18}F-FDG PET/CT is the key modality in the evaluation of treatment response in patients with MM. These novel imaging techniques not only increase the sensitivity and specificity of MM diagnosis but also provide reliable prognostic information. Further advancements in current imaging techniques will have beneficial impacts on the management of MM in the future. However, to understand and utilize these imaging techniques effectively, it is important to better understand the biology of MM itself. The management of MM is a complex process requiring

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a multidisciplinary approach, and radiologists must be cognizant of both the oncological and diagnostic imaging advances in relation to this cancer to utilize them to their maximum potential.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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