Multiple myeloma is the most common primary bone cancer among U.S. adults aged 70 years and older, and the incidence of the disease is increasing. Despite significant advances in treatment since the 1960s, multiple myeloma remains a challenging disease to diagnose and treat. Several medical diagnostic imaging examinations play important roles. This article reviews the biological basis of multiple myeloma, clinical features and diagnosis of the disease, and imaging and treatment protocols. The article also discusses unusual presentations of multiple myeloma.

Multiple myeloma is responsible for approximately 10% of all blood-related cancers, and an estimated 20,000 new cases are diagnosed in the United States each year. It is the most common primary bone cancer among adults. Epidemiologists project that incidence of multiple myeloma will continue to increase as baby boomers age because the disease occurs most often among people aged 70 years and older.

Multiple myeloma is associated with high morbidity and mortality levels. The first documented case of myeloma was diagnosed in 1845 in London by Dr William MacIntyre, who observed an abnormal protein in a patient’s urine. Dr Henry Bence Jones further investigated the patient’s urine and published his findings in 1848. The first documented medical records of myeloma referred to the disease as “mollities and fragilatas ossium,” or soft and fragile bones. A surgeon named John Dalrymple subsequently determined that the diseased bones contained plasma cells. The term multiple myeloma was introduced in 1873 to describe the presence of multiple plasma cell sores in bone.

Incidence and Risk Factors

The average age of a multiple myeloma patient at diagnosis is 60 years. Multiple myeloma represents nearly 1% of all cancers found in North American whites and Asians. Blacks are almost twice as likely as either whites or Asians to develop multiple myeloma. Generally, men have a 50% greater risk for developing multiple myeloma than women do. Asian Pacific Islanders have the lowest incidence followed by whites and Hispanics, with a slightly higher incidence among American Indian/Alaska Natives. Figure 1 shows the incidence and mortality rate for both sexes by race within the United States from 1975 to 2010. The graphs clearly show the rate of incidence stabilizing for all races except blacks.
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The greatest drop in mortality since 1995 has occurred among blacks, however. With the exception of a syndrome called monoclonal gammopathy of undetermined significance (MGUS), there is no known cause or risk factor for multiple myeloma. Several studies show strong empirical evidence, however, of a significant positive association between body mass index (BMI) and an increased risk of multiple myeloma. The Million Women Study in the United Kingdom involved a cohort of more than 1.2 million women aged between 50 and 64 years whose cases of multiple myeloma were followed for 5 years. It reported a relative risk for multiple myeloma of 1.31 per 10 units of increase in BMI. Based on a follow-up of 10 cohorts totaling 5.1 million men and women for a mean of 14.6 years, 4273 cases of multiple myeloma in men and 3664 cases in women were analyzed and showed a direct positive relation between BMI and multiple myeloma. The relative risk of multiple myeloma was 1.11 for both men and women who had a 5 kg/m² increase in BMI over the 14-year study period.

Figure 1. Surveillance, Epidemiology, and End Results (SEER) program incidence and U.S. death rates for myeloma, both sexes. Incidence data for whites and blacks are from the SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta). Incidence data for Asian/Pacific Islanders (API), American Indians/Alaska Natives (AI/AN), and Hispanics are from the SEER 13 areas (SEER 9 areas, San Jose–Monterey, Los Angeles, Alaska Native Registry, and rural Georgia). Mortality data are from U.S. Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention. Reprinted from National Cancer Institute SEER Web site. http://seer.cancer.gov/csr/1975_2010/browse_csr.php?sectionSEL=18&pageSEL=sect_18_zfig02.html. Accessed December 1, 2013.

* Rates are age-adjusted to the 2000 U.S. Std Population (19 age groups—Census P25-1103). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute. Joinpoint analyses for whites and blacks during the 1975-2010 period allow a maximum of 5 joinpoints. Analyses for other ethnic groups during the period 1992-2010 allow a maximum of 3 joinpoints.

* Rates for AI/AN are based on the Contract Health Service Delivery Area counties.

* Hispanic is not mutually exclusive from whites, blacks, API, and AI/AN. Incidence data for Hispanics exclude cases from Connecticut, the District of Columbia, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, South Carolina, Oklahoma, and Vermont.
MGUS is the most influential predictor of myeloma, and some physicians believe that it is an early form of the disease.\(^3\) When a patient has MGUS, it is considered precancerous, and although the number of myeloma cells is higher than normal, they still make up fewer than 10% of all bone marrow cells. A patient with MGUS usually is unaware of the disease, and MGUS can lead to diseases other than multiple myeloma, such as lymphoma.\(^2,3\)

Occurring in approximately 3% of people aged 70 years and older, MGUS progresses to multiple myeloma in 25% of diagnosed cases.\(^2\) A family history of myeloma or MGUS has been documented in 3% to 5% of all myeloma diagnoses.\(^2\) Workers who constantly are exposed to oil products such as those used in furniture manufacturing and the petroleum industry have a significantly higher risk of developing multiple myeloma, although the actual occurrence is extremely small.\(^6\) Exposure to high levels of radiation is a significant risk factor for multiple myeloma. Japanese survivors of World War II atomic bombs are 10 times more likely to have myeloma or leukemia than Japanese residents outside the bombed area in the same age groups.\(^6\)

Researchers also have observed an increasing trend of myeloma in people younger than 55 years of age, which implies significant environmental factors contributing to risk for the cancer in the past 60 years. For example, consuming contaminated seafood might be a risk factor.\(^3\) Although the exact causes and risk factors are unknown, a substantial body of ongoing research is analyzing possible risk factors, including genetic risk.

**Biology**

Normal plasma cells are found in the bone marrow; the bone marrow is considered a generative lymphoid organ because it is the incubator of B cells, a type of lymphocyte, and all blood cells. B lymphocytes mature into plasma cells, which make and release antibodies. Once lymphocytes mature, they move into the blood and certain parts of lymphoid organs. Lymphocytes circulate constantly in tissues, moving to sites that are infected or inflamed. Myeloma results when malignant plasma cells (myeloma cells) build up in the bone marrow, causing fewer red blood cells, white blood cells, and platelets to form. The myeloma cells weaken and damage the bone.\(^3\)

Scientists are unclear on the earliest events that cause a plasma cell to transform into a myeloma cell, but they know that myeloma cells originate from a single B cell that once resided in the lymph node or spleen. When hematologists place a biopsy sample of bone marrow containing myeloma cells under a microscope, they find an abnormal number of plasmalike cells with gross changes in their chromosomes. There also are an unusually high number of mutations in antibody genes, which appear to occur within the somatic hypermutation event, the last phase of genetic fine tuning before a cell transforms into a plasma cell.

Most myeloma cells have an extra chromosome or chromosome trisomy instead of the normal 22 pairs. The reason is translocation, an abnormality that confuses chromosomes when a portion of one chromosome (4, 6, 11, 16, or 20 in the case of multiple myeloma) breaks off and reattaches to a different chromosome. The translocation to an antibody-heavy chain gene located on chromosome 14 is the initial visible development in the transformation of a normal plasma cell into a myeloma cell and can be detected in MGUS. There is speculation among some scientists that these chromosomal abnormalities cause uncontrollable cell growth resulting in the failure of the normal mechanisms that signal a plasma cell to stop dividing. Multiple myeloma derives from this B cell precursor with continuous clonal evolution or continual growth from a single clone of a B cell.\(^3\)

Plasma cells normally account for approximately 5% of bone marrow. The proliferation of myeloma cells causes overcrowding and damage to healthy bone tissue. Nearly 80% of myeloma patients have a high concentration of an abnormal plasma cell that manufactures monoclonal proteins (M protein). The M protein also is referred to as the *M-spike* because of its appearance on protein electrophoresis. Within advanced stage myeloma, the M protein increases to 5 times the amount normally found in blood (from 1 g to 5 g per 3 oz of blood). The M protein is deposited into urine and into blood serum, which is the liquid portion of blood that remains after removal of red blood cells. M proteins are immunoglobulin molecules that cannot function as normal antibodies to fight infections.

Immunoglobulins comprise 5 types of heavy chains (IgG, IgA, IgM, IgD, IgE) and 2 types of light chains (κ, λ). Ten possible combinations of heavy and light chains
are thus possible (IgGκ, IgGλ, etc), and protein electrophoresis is able to detect all of them. Normal plasma cells produce separate heavy and light chains that are later assembled to form an intact immunoglobulin. This always results in an excess of light chains; the free light chains are reabsorbed mostly by the kidneys.

If an M protein is present in the blood serum, the number of monoclonal free light chains is too high for the kidneys to absorb, resulting in excess Bence Jones proteins in the blood and urine.\textsuperscript{3,4} Approximately 75% of multiple myeloma patients have high amounts of Bence Jones proteins. Excessive M protein thickens blood, reducing blood flow to the brain and causing headaches and blurred vision or bruising and nose bleeds. Blood clots can form in the arms, legs, kidneys, eyes, and heart, leading to kidney problems, vision loss, heart disease, and numbness within the arms and legs from nerve damage. The high amount of M proteins is the first concrete evidence that a patient has myeloma or MGUS. The most common type of M protein manufactured by myeloma cells is IgG and the second most common is IgA. IgG is found more often in bone marrow, whereas IgA is found more often in blood.

In the disease’s initial stage, myeloma lesions are found in only 1 or 2 sites on radiographs. Physicians refer to this as the intramedullary (inside the bone) stage. With disease progression, the bone marrow excretes myeloma cells, which circulate and lodge in bone cavities throughout the body. This is the extra-medullary (outside the bone) or extraosseous stage and is associated with a poor prognosis. Detecting the presence of extraosseous multiple myeloma in the initial diagnosis and follow-up is essential.\textsuperscript{1,3}

The Durie and Salmon Staging System (see Table 1) has been used since 1975 worldwide and remains a standard for assessing prognosis and classifying a patient for clinical trials and historical comparisons of published results. The Durie and Salmon Staging System correlates clinical diagnostic criteria with the measured myeloma cell mass. Prognosis is based on the quantity and specific properties of myeloma cells; cell properties include the myeloma cells’ growth rate, production rate of M proteins, and the production of various combinations of lymphokines and chemicals that damage body organs, tissues, and functions.\textsuperscript{4}

<table>
<thead>
<tr>
<th>Table 1</th>
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**Durie and Salmon Staging System**\textsuperscript{9}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Measured Myeloma Cell Mass (cells x 10\textsuperscript{12}/M\textsuperscript{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (A or B)</td>
<td>All of the following:</td>
<td></td>
</tr>
<tr>
<td>low cell mass</td>
<td>• Hemoglobin value &gt; 10 g/dL</td>
<td></td>
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<tr>
<td></td>
<td>• Serum calcium value normal or &lt; 12 mg/L</td>
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<tr>
<td></td>
<td>• On bone radiograph, normal bone structure (scale 0), or solitary bone plasmacytoma only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low M-component production rate IgG value &lt; 5 g/L; IgA value &lt; 3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bence Jones protein &lt; 4 g/24 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6-1.2</td>
<td></td>
</tr>
<tr>
<td>Stage II (A or B)</td>
<td>Fitting neither stage I nor stage III criteria.</td>
<td></td>
</tr>
<tr>
<td>intermediate cell mass</td>
<td>0.6-1.2</td>
<td></td>
</tr>
<tr>
<td>Stage III (A or B)</td>
<td>One or more of the following:</td>
<td></td>
</tr>
<tr>
<td>high cell mass</td>
<td>• Hemoglobin value &lt; 8.5 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum calcium value &gt; 12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advanced lytic bone lesions (scale 3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High M-component production rate IgG value &gt; 7 g/dL; IgA value &gt; 5 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bence Jones protein &gt; 12 g/24 h</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: Ig, immunoglobulin; M-component, monoclonal protein component.
The symptoms and complications of myeloma also stem from the disease’s influence on adjoining bone cells, leading to bone loss or fractures and abnormal increases in blood calcium from lost bone tissue. Healthy bones constantly repair and rebuild themselves. Osteoclasts are the cells that break down and remove old, weakened bone, and osteoblasts develop new bone by replacing weak spots with calcium and minerals. Normally this process is in perfect balance, but myeloma cells cause osteoclasts to be hyperactive and accelerate bone loss. Simultaneously, myeloma cells stimulate bone marrow stromal cells to produce growth factors, or lymphokines, which promote myeloma cell growth.1

The 3 most important myeloma-growth lymphokines, vascular endothelial growth factor, tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6), promote development of new blood vessels that supply myeloma cells with necessary oxygen and nutrients. Together, IL-6 and TNF-α cause myeloma cells to grow more rapidly and spread to other bones. When TNF-α is overproduced, it can cause white blood cells to die and lower red blood cell production by blocking the hormone erythropoietin. This loss of red and white blood cells causes anemia and a reduction in the immune system’s ability to ward off infection. After initial bone loss, infections are the second most common complication of myeloma.2

Clinical Features and Diagnosis

MGUS is recognized as a potential precursor to multiple myeloma but is a benign condition.8 Three types of myeloma are solitary plasmacytoma, smoldering or asymptomatic myeloma, and symptomatic or active myeloma.10 A bone marrow aspirate of fluid and biopsy of bone tissue are necessary to stage the disease accurately and establish a treatment regimen.3

In the early stage of multiple myeloma, patients usually report overall fatigue or generalized complaints during a routine medical examination. The physician reaches a diagnosis of multiple myeloma following laboratory test results from a complete blood count, serum biochemistry, and serum and urine electrophoresis, along with a metastatic bone survey.2,11 Blood also is checked for clotting time, calcium, creatinine, and albumin levels and for lactate dehydrogenase to determine potential tissue damage. The physician might examine the patient to determine proper nerve function, muscle contraction, and heart rhythm maintenance.2

In healthy people, nearly all calcium is found in the bones and very little is released into the blood and urine. When multiple myeloma causes osteoclasts to break down bone, excess calcium is released into the blood, resulting in hypercalcemia. About 30% of multiple myeloma patients have hypercalcemia, which reduces kidney function because of the toxic effect of high calcium levels on the kidneys. The condition also causes the patient to experience constant thirst and the need to urinate.2 Creatinine is a metabolic waste product removed from the body by the kidneys. High creatinine levels indicate that the kidneys might not be functioning properly.3

The next stage of the disease involves lower back or rib pain or severe sudden pain from a vertebral fracture or compression. Advanced stage myeloma usually consists of anemia, persistent fatigue, weight loss, decreased appetite, bone pain and loss, weakness or numbness in the legs, bacterial infections, low white blood cell count, mental confusion, and increased thirst and urge to urinate. The occurrence and extent of these symptoms varies among patients and can be mistaken for other diseases.12

Two relatively new blood tests have been added to the tools available for detecting and monitoring myeloma. Beta-2 microglobulins (beta-2m) ordinarily are found on the surface of white blood cells and discarded into the blood in small amounts. When proliferating myeloma cells destroy white blood cells in bone marrow, beta-2m is released into the blood. The increased beta-2m blood level indicates the number of myeloma cells in the bone marrow.12

The other test measures albumin, which is made by the liver and excreted into the blood. Albumin is a blood transporter of hormones and other small molecules. The blood albumin level indicates a patient’s overall health. A low albumin level indicates a worsening health status. Combining the beta-2m and albumin serum values has become part of the 3-part International Staging System (ISS; see Box).12

The ISS was tested on more than 10 000 patients in North America, Europe, and Asia. It was validated on a population representing patients aged younger and older than 65 years and among patients treated
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by standard therapies or through autologous stem cell transplantation, a procedure in which patients receive their own stem cells. Developers of the ISS also validated it through comparison with the Durie and Salmon Staging System. The ISS is available worldwide and has been incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma, along with the Durie and Salmon Staging System criteria.

A less commonly used blood test is for C-reactive protein. Also produced by the liver, C-reactive protein is found in large amounts when the myeloma growth factor IL-6 is at a high level. Because IL-6 causes myeloma cells to proliferate and in turn leads to production of C-reactive protein, C-reactive protein serves as a surrogate indicator of IL-6 and myeloma growth and as a prognostic indicator for multiple myeloma. Table 2 lists the recommended diagnostic and staging criteria for multiple myeloma. Imaging test results are included in the diagnostic criteria. Table 3 summarizes the routine blood tests and their significance.

Tests for more complex prognostic factors for multiple myeloma exist but are not routinely available or are too costly to perform on a regular basis. These include the plasma cell labeling index, a percentage index in which a low level of plasma cells indicates a better prognosis than a high number. The plasma cell labeling index requires a recently acquired bone marrow or blood sample be taken and tested at the Mayo Clinic. A chromosome analysis involving standard studies, or FISH (fluorescent in situ hybridization), also can be conducted on bone marrow samples. Extra or translocated chromosomes suggest a more limited response to treatment and poorer prognosis.

A research technique called molecular array analysis checks for active genes that may correspond with a positive or negative prognosis. The technology allows researchers to build a microchip to test the activation of specific genes. This enables them to find the specific gene or set of genes that significantly contribute to disease progression or damage to organs caused by disease. The research strategy has been used to compare patients without myeloma to those who have 3 or more lesions. Results show a distinct pattern of important genetic differences in tumor biology that potentially could focus research on new therapeutic targets. Specifically, the inhibitor protein Dkk-1 was found in myeloma and linked to activating genes that cause osteoblasts to shut down. The results were confirmed in a comparison of myeloma patients’ bone marrows with gene activation. So far, molecular array analysis has been used only in research and not for routine diagnosis or management.

Box

**International Staging System**

Staging systems for cancer quantify the extent of disease in the body. Although the Durie and Salmon Staging System has been the most commonly used system for staging multiple myeloma, the International Staging System (ISS) classification method was developed in 2005. The ISS combines serum β² microglobulin and serum albumin levels to provide a reproducible 3-stage classification for multiple myeloma:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum β² microglobulin &lt; 3.5 mg/L, serum albumin &gt; 3.5 g/dL</td>
</tr>
<tr>
<td>II</td>
<td>Not I or III; serum β² microglobulin &lt; 3.5 mg/L, but serum albumin &lt; 3.5 g/dL or serum β² microglobulin 3.5-5.5 mg/L irrespective of the serum albumin</td>
</tr>
<tr>
<td>III</td>
<td>Serum β² microglobulin &gt; 5.5 mg/L</td>
</tr>
</tbody>
</table>

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Diagnostic Imaging

The existence of one or more focal lesions on a metastatic bone survey (also called a skeletal bone survey) remains the standard imaging indicator for a diagnosis of multiple myeloma and for initial staging according to the classic Durie and Salmon Staging System. Use of cross-sectional and functional imaging techniques now plays an increasingly important role, however, in the diagnostic workup and staging of the disease. An expanded Durie-Salmon PLUS system incorporates advanced imaging technologies. Each modality has specific strengths and weaknesses in the diagnosis, staging, and management of multiple myeloma.

The imaging modalities used to evaluate multiple myeloma can be categorized into 2 groups: anatomic or structural modalities and functional imaging.
Table 2

International Myeloma Working Group Criteria for the Diagnosis of Myeloma and Guidelines for the Diagnostic Workup of Myeloma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnostic Criteria (All 3 Required)</th>
</tr>
</thead>
</table>
| **Symptomatic multiple myeloma**       | - Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma  
- Monoclonal protein present in the serum and/or urine  
- Myeloma-related organ dysfunction (≥ 1)  
  - [C] Calcium elevation in the blood (serum calcium ≥ 10.5 mg/L or upper limit of normal)  
  - [R] Renal insufficiency (serum creatinine > 2 mg per 100 mL)  
  - [A] Anemia (hemoglobin < 10 g per 100 mL or 2 g < normal)  
  - [B] Lytic bone lesions or osteoporosis |
| **Monoclonal gammopathy of undetermined significance (MGUS)** | - Serum monoclonal protein low  
- Monoclonal bone marrow plasma cells < 10%  
- No evidence of end-organ damage attributable to the clonal plasma cell disorder:  
  - Normal serum calcium, hemoglobin level and serum creatinine  
  - No bone lesions on full skeletal survey and/or other imaging if performed  
  - No clinical or laboratory features of amyloidosis or light chain deposition disease |
| **Smoldering or indolent myeloma**      | - Monoclonal protein present in the serum 3 g per 100 mL or higher or  
- Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy  
- No evidence of end-organ damage attributable to the clonal plasma cell disorder:  
  - Normal serum calcium, hemoglobin level and serum creatinine  
  - No bone lesions on full skeletal survey and/or other imaging if performed  
  - No clinical or laboratory features of amyloidosis or light chain deposition disease |
| **Solitary plasmacytoma of bone**       | - Biopsy-proven plasmacytoma of bone in a single site only. Radiographs and magnetic resonance imaging and/or  
  - Fludeoxyglucose F 18 positron emission tomography imaging (if performed) must be negative outside the primary site  
  - The primary lesion may be associated with a low serum and/or urine monoclonal component  
  - The bone marrow contains no monoclonal plasma cells  
  - No other myeloma-related organ dysfunction |

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- These criteria identify stage IB and stages II and III A/B myeloma by Durie-Salmon stage. Stage IA becomes smoldering or indolent myeloma.
- If no monoclonal protein is detected (nonsecretory disease), then more than 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
- A variety of other types of end-organ dysfunctions occasionally can occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.
- If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then more than 30% plasma cells are required in the bone marrow.
- Low is defined as serum M protein less than 3 g per 100 mL.
- These criteria identify Stage IA myeloma by Durie-Salmon stage.
Typically, air, dense organs, and gastrointestinal tract contents can mimic or conceal focal osteolytic lesions. The effectiveness of a metastatic bone survey also is limited because at least 50% of bone loss must occur before a focal lesion can be seen on a radiograph. This is especially true in the vertebral column. Consequently, an intramedullary tumor only is visible if it produces either focal osteolysis, bone tissue degeneration, or secondary findings such as pathologic fracture. Figure 2 demonstrates the limitations of a metastatic bone survey compared with 18F-FDG PET-CT and CT of the lumbar spine. A metastatic bone survey is altogether useless for extramedullary myeloma. However, the metastatic bone survey remains preferable to other imaging techniques for detecting minute, subcentimeter focal osteolytic lesions of the distal extremities (hands, feet, or forearms). Bone lesions never heal, so a metastatic bone survey cannot be used for monitoring post-treatment responses and is useful only for revealing relapse if new evidence of disease criteria occurs. A metastatic bone survey is more useful than MR imaging for patients who have had surgery to implant joint prostheses, spinal fusion hardware, or vertebroplasty cement because these materials appear as artifacts on MR images. If a whole-body 18F-FDG PET-CT or a whole-body musculoskeletal CT can be acquired, the metastatic bone survey may be unnecessary and is no longer cost-effective for staging and restaging of the disease.

Magnetic Resonance Imaging

MR imaging for multiple myeloma has been well established and documented since the 1980s. MR imaging provides excellent soft-tissue contrast resolution and can help evaluate focal marrow disease from multiple myeloma, often identifying focal lesions missed on radiography. On T1-weighted images, marrow lesions associated with multiple myeloma generally appear as deposits of decreased fat and increased signal intensity. Using T2 weighting and short T1 inversion recovery (STIR) techniques can provide greater sensitivity for imaging marrow than can T1 weighting alone. On an MR image, appearance of normal hematopoietic marrow depends largely on a patient’s age. A younger patient’s marrow has a more cellular appearance because of less fat tissue and more blood and
made in the context of medication use or chemotherapy rebound. The MR technologist acquiring the images should ensure that thorough patient histories include all treatment details.

Although MR is sensitive in identifying possible multiple myeloma, a major limitation of MR imaging is its specificity. Most musculoskeletal tumors have similar signal intensities on MR imaging and cannot be distinguished from multiple myeloma. Further, MR images can show focal or diffuse patterns that could represent normal variations in the physiological process of a patient’s marrow. MR must be accompanied by laboratory tests for diagnosis, and depending on the appearance of focal lesions on MR alone can lead to understaging or overstaging of the disease.

Regardless, MR is useful as a staging tool, helping to differentiate solitary plasmacytoma of bone from multiple myeloma and to record the characteristics of diffuse marrow infiltration. Compared with 18F-FDG PET, MR provides superior spatial and contrast resolution. MR slices generally are 2 mm for a high-field system vs approximately 5 mm for the PET portion of newer PET-CT scanners. MR equipment is more widely available than PET-CT equipment. When used for therapy monitoring, 18F-FDG PET-CT has a higher false-negative rate than MR for some patients just released from treatment. MR also is clearly superior to all modalities for an early diagnosis of avascular necrosis.

MR images also can reveal lesions that have reached soft tissues by breaking through the bony cortex. Other MR findings that appear in patients with multiple myeloma include vertebral or sacral fractures, discitis infection, avascular necrosis of femoral or humeral heads as a result of dexamethasone therapy, and osteonecrosis of the maxilla or mandible associated with bisphosphonate use.

Although dedicated focal MR imaging of the skull, pelvis, spine, or extremities is used widely for multiple myeloma evaluation and correlates with staging systems, use of whole-body techniques has magnified the role of MR in multiple myeloma imaging. Focal MR imaging concentrates mostly on the bone marrow of the axial skeleton, but whole-body MR imaging that includes at minimum the proximal appendicular skeleton has emerged as the most sensitive imaging modality for detecting diffuse and focal multiple myeloma.

Figure 2. False-negative metastatic bone survey. Focal osteolytic lesions of multiple myeloma are seen well with 18F-FDG PET-CT compared with the metastatic bone survey. A. Lateral projection of lumbar spine demonstrates no evidence of tumor. B. Lateral 18F-FDG PET-CT image reveals diffuse myeloma marrow infiltration (short arrows). C. Axial CT-only images showing focal lytic bone lesions of L3 and L4 (long arrows). D. Axial PET-CT fused images. Reprinted with permission from Epstein J, Walker R. Myeloma and bone disease: “the dangerous tango.” Clin Adv Hematol Oncol. 2006;4(4):300-306.

blood-forming tissues. People who are middle-aged to elderly, the majority of multiple myeloma patients, have more fatty tissue and less hematopoietic elements. An understanding of this typical age-adjusted variation is necessary to interpret MR findings accurately.

Marrow spaces are defined on MR images as homogeneous, heterogeneous, or variegated. The literature has reported several pattern descriptions of multiple myeloma infiltrations on MR images. These include normal marrow, a variegated (also called micronodular or salt-and-pepper) pattern, and a diffuse pattern. These patterns have been related to the Durie and Salmon Staging System for purposes of staging and prognosis. For example, normal and variegated patterns correlate to stage I disease.

Because malignant tumors need an enhanced blood supply to survive, postcontrast T1-weighted images display an increase in T1 signal with the affected marrow appearing bright relative to normal skeletal muscle and to precontrast T1-weighted images. Certain marrow-stimulating medications or recovery from recent chemotherapy produce a diffuse change in the marrow signal. The interpretation of diffuse findings should be
Studies comparing whole-body MR imaging to PET and multidetector CT demonstrated higher sensitivity for detection of multiple myeloma with MR. The MR techniques used included T1-weighted and STIR imaging. Multiple sequences are recommended to identify focal or diffuse disease. Spin-echo sequences, both T1-weighted and T2-weighted, gradient-echo (T2*-weighted), and STIR are typical sequences for whole-body MR imaging to evaluate multiple myeloma. Diffusion-weighted imaging methods also are being studied.1,17

When MR imaging is used in follow-up or surveillance imaging of multiple myeloma, MR-defined focal lesions can be concealed by effects on marrow caused by chemotherapy rebound. Effective treatment quickly normalizes the diffuse marrow signal, but focal lesions return much more slowly. The concealed MR-defined focal lesions become evident over time as the diffuse signal clears with periodic MR examinations. This is called unmasking of the lesions and should not be interpreted as disease progression.13

The literature also proposes use of contrast-enhanced spin-echo sequences, with and without fat suppression for whole-body MR imaging.1 Use of gadolinium contrast enhancement is not routine practice in evaluating bone marrow for multiple myeloma diagnosis and management because use of the contrast agent does not significantly add to the radiologist’s ability to identify additional lesions. Gadolinium-based contrast agents have been linked to the development of nephrogenic systemic fibrosis in patients who have compromised renal function. The risks of using gadolinium in patients with multiple myeloma must be weighed against potential benefits.17,18

MR imaging uses no ionizing radiation and its correlation with prognostic indication of survival has led to inclusion of MR scan results in the Durie-Salmon PLUS system.18 In addition to limited sensitivity, MR can be contraindicated in patients who have implanted pacemakers, defibrillators, neural stimulators, cochlear devices, certain prosthetic heart valves, and intracranial aneurysm clips. Even when an MR examination is deemed safe, implanted devices can interfere with image quality.

The relative length of MR imaging can produce breathing-related motion artifacts in the rib area that can hide small lesions. The full expense of an MR examination is also much higher in the United States than PET or 18F-FDG PET-CT.13

Nuclear Medicine Imaging

PET imaging can identify multiple myeloma lesions because of the lesions’ high metabolic rate and high glucose demand.1 Use of 18F-FDG PET-CT can identify metabolic activity of bone and marrow lesions and is helpful for evaluating extramedullary signs of the disease and for quantifying metabolic activity in bone marrow. The addition of CT provides high-resolution imaging of the bone and resulting evaluation of lytic bone lesions that is superior to evaluation with radiography.17

Active multiple myeloma focal lesions are well-defined areas of increased uptake on PET images. Findings must be greater than 5 mm in diameter to be diagnosed as a focal lesion. Multiple solitary plasmacytomas without marrow infiltration require image-guided biopsy with CT to diagnose correctly. Solitary plasmacytoma needs to be distinguished with 18F-FDG PET-CT, additional MR images, or a central marrow biopsy. Additional tumor sites often are seen on PET images. It is crucial to determine the precise number of plasmacytomas because patients with solitary plasmacytomas seldom require systemic treatment.13

Figure 3 compares a breakout lesion and extramedullary disease within the same patient on 18F-FDG PET-CT images. The number of focal lesions on radiographs, MR scans, or 18F-FDG PET-CT is significantly and inversely related to both long-term and event-free survival. Explicitly, the number of focal lesions identified on MR or PET correlates with patient outcome. Historical comparisons of all imaging examinations are necessary to track progressions or relapse.13

The 18F-FDG PET imaging protocols are structured to image all bone marrow space and soft tissues of the body. The scan must encompass the patient’s anatomy from the top of the skull to the feet. Some scanners require more than one examination to cover the entire anatomy. It also is essential to measure and document the patient’s serum glucose level when administering the radioisotope injection. The high serum glucose level of multiple myeloma patients is caused by the frequent use of high-dose glucocorticoid medications.19 The medications interfere with image.
Reisenbuckler

quality by inhibiting fludeoxyglucose F 18 uptake. Insulin use to lower blood glucose affects PET scans by diverting fludeoxyglucose F 18 into both bony muscle and the liver. Physical exercise can have a similar effect from increased muscle uptake caused by glycogen replenishment. Therefore, patients should be instructed to limit physical activity and adhere to a diet that is low in carbohydrates and high in proteins for 24 hours before having a PET or 18F-FDG PET-CT scan. PET technologists should inquire about and document all medications, diet, and physical activities before beginning imaging examinations.¹³

Brown adipose tissue potentially can degrade image quality in 18F-FDG PET-CT scans. This typically is seen in premenopausal women and men younger than aged 30 years.¹³ Brown adipose tissue is distributed within the neck, shoulders, mediastinum, and upper retroperitoneal and paravertebral regions and contains more capillaries than white fat. Brown adipose tissue can cause severe focal, nodular, and intense fludeoxyglucose F 18 uptake and possibly obscure tumor uptake. The correlating CT scan of a brown adipose tissue area on an 18F-FDG PET-CT image shows normal adipose tissue. However, if an imaging center has a PET scanner only, there is no corresponding anatomical information from the CT scanner. If a CT scan shows an area of abnormal density or a previous tumor along with brown adipose tissue uptake, the differentiation between brown adipose tissue uptake and tumor recurrence is difficult. In these instances, premedications such as anxiolytic agents (eg, diazepam or alprazolam) have proved useful in blocking brown adipose tissue activation.¹³

**Other Nuclear Medicine Imaging**

A technetium Tc 99m sestamibi bone scan, or Tc 99m MIBI imaging, has limited use in evaluation of multiple myeloma. The technique can help differentiate MGUS from symptomatic multiple myeloma and disease manifestation. The uptake of technetium Tc 99m sestamibi correlates to the consolidation of mitochondria within cells. Therefore, areas of elevated metabolic activity cause increased uptake. Areas of high technetium Tc 99m sestamibi uptake are the myocardium, liver, and spleen.

SPECT or SPECT-CT imaging can overcome a limitation of Tc 99m MIBI imaging related to technetium Tc 99m sestamibi excretion in the bile that affects image quality of the heart, liver, spleen, and bowel regions. Technetium Tc 99m sestamibi uptake can be blocked by drug-resistant tumors, producing a false-negative scan.¹³ If focal lesions are evident, Tc 99m MIBI imaging can be used to evaluate disease distribution or additional areas of involvement.¹³ Tc 99m MIBI imaging is less expensive and more readily available than 18F-FDG PET or 18F-FDG PET-CT and can be used when PET scanning is unavailable.¹³

**Clinical Relevance of Imaging in Multiple Myeloma**

It is necessary for staging systems and clinical guidelines to incorporate advanced imaging to stage and restage multiple myeloma accurately.¹³ The Durie-Salmon PLUS system has been adapted to incorporate cross-sectional information, and National Comprehensive Cancer Network guidelines recommend additional imaging examinations, including MR, CT, or 18F-FDG PET-CT in some circumstances.¹⁰,¹⁷ Medical imaging helps to identify sites for image-guided biopsies.
In the United States, the Centers for Medicare & Medicaid Services has approved broad-coverage reimbursement for multiple myeloma imaging of Medicare recipients with the following modalities and purposes: 18F-FDG PET-CT for “initial treatment strategy” (initial diagnosis and staging) and 18F-FDG PET-CT examinations for “subsequent treatment strategy” (restaging). The Centers for Medicare & Medicaid Services recommends CT to confirm metastatic bone survey findings or changes except for the upper skull and extremity regions. Neither a metastatic bone survey nor a whole-body musculoskeletal CT can determine whether an osteolytic lesion contains active myeloma. Therefore, anatomic imaging is secondary to functional imaging for managing treatment or guiding biopsies.13

**Treatment**

Treatment options for multiple myeloma vary and depend upon baseline evaluations, cytogenetic features of the myeloma cells, and the patient’s age. The International Myeloma Working Group has recommended specific uniform criteria to classify response to treatment. Reductions in the plasma cells or monoclonal protein should be correlated with documentation of clinical improvement (ie, bone pain reduction or increased red blood cell count). There are 5 categories of responsiveness, including stringent complete response, complete response, very good partial response, partial response, and stable disease (see Table 4).5,10,21

Occult infections often are the source of morbidity and mortality in multiple myeloma patients. Moreover, diagnosing infections in multiple myeloma patients often is complicated by tumor-related fevers and the chronic use of high-dose glucocorticoid and pain medications. Malphalan-based myeloablation in preparation for stem-cell transplantation often results in significant neutropenia and immunosuppression, which reduces the efficacy of radiolabeled leukocyte scans in diagnosing infection sites. An abrupt increase in C-reactive protein also suggests an infection.13

The use of 18F-FDG PET-CT is preferable for the detection of occult infection. Possible infections include septic thrombophlebitis of venous catheters, sinusitis, pneumonia, osteomyelitis, discitis, cellulitis, mastoiditis, and genitourinary or gastrointestinal tract infections. Periodontal abscesses are common and must be differentiated from tumor involvement or osteonecrosis of the mandible or maxillae.18 The 18F-FDG PET-CT is crucial to patient management because the examination can assist in identifying the existence and sites of possible infections, along with their extent. The presence, extent, and location of infections can alter diagnosis or therapeutic approach.13

In the United States, the Centers for Medicare & Medicaid Services has approved broad-coverage reimbursement for multiple myeloma imaging of Medicare recipients with the following modalities and purposes: 18F-FDG PET-CT for “initial treatment strategy” (initial diagnosis and staging) and 18F-FDG PET-CT examinations for “subsequent treatment strategy” (restaging). The Centers for Medicare & Medicaid Services recommends CT to confirm metastatic bone survey findings or changes except for the upper skull and extremity regions. Neither a metastatic bone survey nor a whole-body musculoskeletal CT can determine whether an osteolytic lesion contains active myeloma. Therefore, anatomic imaging is secondary to functional imaging for managing treatment or guiding biopsies.13

**Table 4**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response</td>
<td>Reduction in plasma cells or monoclonal protein with clinical improvement</td>
</tr>
<tr>
<td>Complete response</td>
<td>Reduction in plasma cells or monoclonal protein without clinical improvement</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>Slight reduction in plasma cells or monoclonal protein with clinical improvement</td>
</tr>
<tr>
<td>Partial response</td>
<td>No significant reduction in plasma cells or monoclonal protein</td>
</tr>
<tr>
<td>Stable disease</td>
<td>No change in plasma cells or monoclonal protein</td>
</tr>
</tbody>
</table>

When residual disease exists, the remaining myeloma cells might relapse. The propensity to relapse depends on the remaining cells’ molecular characteristics. If clinical relapse does not occur, then the plateau phase has been reached, and the disease is stable. The time span from initial treatment to the plateau phase varies from 3 to 6 months to 12 to 18 months.4 In general, a relapse is reached when a patient is categorized in at least partial response for at least 6 months. If a patient has MGUS or smoldering myeloma, immediate treatment is not required. A patient requires therapy only when the disease has advanced to symptomatic multiple myeloma or solitary plasmacytoma of bone.22

Four major types of treatment are used to treat multiple myeloma: drug therapy, radiation therapy, immunotherapy, and ancillary therapies. Drug therapy consists of either chemotherapy or novel targeted agents.
using intravenous or oral routes. Chemotherapy drugs target all rapidly dividing cells, and novel targeted agents such as thalidomide, bortezomib, and lenalidomide affect myeloma cells only. Radiation therapy manages symptoms from localized areas of myeloma involvement, such as the spine. Immunotherapy involves the use of stem cell transplants to stimulate the patient’s immune system.  

Ancillary therapies are used to relieve, treat, or prevent complications of myeloma. Bisphosphonates help protect the skeleton and treat increased blood calcium. Intravenous immunoglobulin treats low levels of normal antibodies and serious infections. Vertebroplasty or kyphoplasty can relieve the pain associated with vertebral fractures.

### Table 4

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stringent complete response</td>
<td>Complete response, plus normal free light chain ratio and absence of clonal cells in bone marrow.</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>Negative immunofixation on serum and urine, along with soft tissue plasmacytoma disappearance and &lt; 5% plasma cells in bone marrow.</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>Serum and urine monoclonal protein detectable by immunofixation but not electrophoresis, or &gt; 90% reduction in serum monoclonal protein plus urine monoclonal protein &lt; 100 mg/24 h.</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>&gt; 50% reduction of serum monoclonal protein and &gt; 90% reduction in 24 h urine monoclonal protein. Measurement and reduction of free light chain levels &gt; 50% if serum and urine monoclonal proteins are not measurable. Plus a &gt; 50% reduction in size of any soft tissue plasmacytoma present at baseline.</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Assigned to patients who do not meet any of the criteria for CR, VGPR, PR, or progressive disease. The stable disease category is not recommended for use as an indicator or response.</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>Increase of &gt; 25% over baseline in one or more of: Serum monoclonal protein component. Urine monoclonal component. Absolute bone marrow plasma cell percentage &gt; 10%. Development of hypercalcemia.</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>Specific indicators of increasing disease or end organ dysfunction. Development of new soft tissue plasmacytomas or bone lesions. 50% (and ≥ 1 cm) increase in size of existing plasmacytomas or lesions. Hypercalcemia &gt; 11.5 mg/dL. Decrease in hemoglobin. Rise in serum creatinine.</td>
</tr>
<tr>
<td>Relapse from CR</td>
<td>Any of the following: Reappearance of serum or urine monoclonal protein. Development of &gt; 5% plasma cells in bone marrow. Appearance of new plasmacytoma, lytic bone lesion, hypercalcemia, or other signs of progression.</td>
</tr>
</tbody>
</table>

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*a This table condenses and summarizes the criteria; see Table 4 sources for complete criteria.

*b Some criteria can be measured as absolute increases vs percentage increases.*
involves a combination of chemotherapy and corticosteroids. The goal is to decrease the number of myeloma cells in the body, thereby relieving symptoms and preventing complications. Recently, corticosteroids have been combined with thalidomide, lenalidomide, or bortezomib in lieu of chemotherapy. Corticosteroids are artificial versions of hormones the body produces normally, most notably cortisol. Corticosteroids are effective for treating myeloma and other bone marrow cancers. Dexamethasone and prednisone are the most commonly used corticosteroids to treat multiple myeloma.

When patients have high doses or prolonged regimens of corticosteroids, adverse effects include elevated blood sugar and blood pressure and weakening of the immune system. Administering pulses of corticosteroids over short periods reduces the risks of adverse effects and increases the medication’s effectiveness.

Melphalan, which was introduced in 1962, was the first chemotherapy agent for treatment of multiple myeloma. Since 1962, various combination therapies have been used to try to improve outcomes for multiple myeloma patients, such as high-dose melphalan chemotherapy along with bone marrow transplants. Stem cell transplants are a rescue therapy for bone marrow stem cells destroyed by high-dose melphalan chemotherapy. Throughout the 1980s and 1990s, melphalan and melphalan plus prednisone combined with stem cell transplants predominated multiple myeloma treatment until the 1997 introduction of thalidomide. Thalidomide can prevent blood vessel growth in tumors and exerts immunomodulatory and antiinflammatory properties. Complete responses were then achievable with one oral agent. More agents rapidly followed: first bortezomib, and then lenalidomide.

If patients are not eligible for a stem cell transplant, the combination regimens of melphalan/prednisone/thalidomide (MPT) or bortezomib/melphalan/prednisone (VMP) are superior to melphalan plus prednisone regimens. Both MPT and VMP are NCCN category 1 choices, meaning the recommendation is based on high-level evidence (eg, randomized trials) with a uniform NCCN consensus. Both MPT and VMP are associated with a risk of peripheral neuropathy. Reducing the frequency of bortezomib to once a week can help minimize the adverse effect.

Drug regimens for patients who are candidates for stem cell transplants have been developed and updated within the past few decades. Specifically, transplant recipients receive combination therapies that include bortezomib, such as bortezomib/thalidomide/dexamethasone (VDT) or bortezomib/lenalidomide/dexamethasone. Other therapies are available, such as a lenalidomide/dexamethasone combination without bortezomib. Physicians should consider harvesting peripheral blood stem cells of patients who will have prolonged exposure to lenalidomide before beginning therapy. Table 5 lists the most frequently used successful drug combinations in the United States.

Stem Cell Transplants

Stem cell transplants are of 2 types; autologous transplants use the patient’s own stem cells, and allogeneic transplants involve matching a donor’s stem cells to those of the patient. Stem cell transplants generally are recommended for patients aged younger than 65 years. High-dose therapy is used in conjunction with autologous stem cell transplantation (ASCT). Autologous transplant has been broadly researched, and some investigators are considering a subset of low-risk patients who could have extended survival and achieve a “functional cure” (complete remission > 4 years). ASCT with high-dose therapy as part of planned frontline therapy that includes treatment strategies before and after transplant has produced cure rates of more than 90%. The addition of antibiotic and supportive care can reduce mortality rates to as low as less than 5%.

Current recommendations suggest considering high-dose therapy ASCT as part of frontline therapy for symptomatic myeloma patients. Peripheral blood stem cells are preferred over bone marrow because the stem cells are relatively easy to acquire and graft more rapidly after transplants.

Planned second autologous transplants should be performed only for patients achieving less than very good partial response with the first transplant. A second transplant can be appropriate for patients who responded well to a first ASCT but relapsed after more than 2 years.

Allogeneic stem cell transplants are much riskier because of potential graft vs host disease and rarely are used alone. The added benefit of tandem or double transplants is unclear. Current recommendations are...
that they be performed at centers specialized to do so.\(^4\) Allogeneic transplant remains a risky procedure with frequent pulmonary complications and a mortality rate of 15% to 30%. Current recommendations do not sanction allogeneic transplants as part of an initial treatment strategy. Miniallogeneic, or nonablative, transplants are performed only within a clinical trial setting. Identical twin, or syngeneic, transplants rarely are used but generally are safe and produce good results.\(^4\)

**Radiation and Supportive Therapy**

Radiation therapy is appropriate and effective for patients with severe local osteolysis and who have pressure on the spinal cord. Adverse effects from radiation therapy include localized damage to normal bone marrow stem cells. Chemotherapy should be used for systemic disease management with localized radiation therapy only in specific myeloma-damaged areas.\(^1\)

Supportive or ancillary therapy for multiple myeloma involves the use of genetically engineered erythropoietin, pamidronate, and zoledronic acid to increase the hemoglobin level of patients with chronic anemia. The combination supportive therapy has demonstrated results, but ongoing research is necessary because myeloma cells have receptors that bind to synthetic erythropoietin.

Bisphosphonates are used for helping patients recover bone density and strength. However, chronic bisphosphonate use can lead to kidney damage and osteonecrosis of the jaw. Fortunately, both of these conditions are uncommon and can be managed by monitoring the serum creatinine level before each dose is administered. Other findings associated with long-term bisphosphonate use are subtrochanteric femur fractures and cancer of the esophagus. In 2010, the U.S. Food and Drug Administration added subtrochanteric femur fractures to its list of precautions and warnings for all bisphosphonate package inserts. Antibiotics only should be used in patients who have active infections and not as a preventive measure.\(^4\)

**Unusual Presentations**

Several documented case histories of unusual sites of extramedullary multiple myeloma have been documented in medical journals. These cases illustrate the complexity of extramedullary multiple myeloma disease progression and the important role that medical imaging plays in diagnosis of the disease.

**Ovarian Involvement**

A 48-year-old woman visited her physician with a one-year history of symptoms involving bone pain, heart palpitations, and significant weight loss. The physical examination revealed mild tenderness in the hypogastic area and weight loss of 22 lb (10 kg) over a 4-month period. Laboratory tests, bone marrow aspiration, and

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**Table 5**

| Frequenty Used Treatment Combinations\(^2\) |
|-------------------------------|-------------------------------------------------|
| **Abbreviation** | **Therapeutic Agent(s)** | **Comments** |
| MP | melphalan/prednisone | Standard treatment for initial therapy |
| CP | cyclophosphamide | Alternative to MP |
| MPT | melphalan/prednisone/thalidomide | Increases efficacy of MP |
| MPL | melphalan/prednisone/lenalidomide | Increases efficacy of MP |
| VMP | vincristine/melphalan/prednisone | FDA approved for frontline therapy |
| VMPT | vincristine/melphalan/prednisone/thalidomide | FDA approved for frontline therapy |
| L | lenalidomide | FDA approved for frontline therapy |
| LVD | lenalidomide/vincristine/dexamethasone | In clinical trials for newly diagnosed and relapsed myeloma |
| CVD | cyclophosphamide/vincristine/dexamethasone | In clinical trials for newly diagnosed and relapsed myeloma |
| BD | bortezomib/dexamethasone | FDA approved for frontline therapy |

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biopsy of the iliac crest indicated more than 60% immature plasma cells. Radiographs displayed osteolytic lesions on the patient’s skull and humeri.

Immunoelectrophoresis revealed a high IgAλ. Stage III multiple myeloma was confirmed. A transvaginal ultrasound revealed bilateral ovarian masses, which were confirmed by a contrast-enhanced pelvic CT scan. Next, a total abdominal hysterectomy and bilateral salpingo-oophorectomy revealed normal ovaries with the exception of a soft papillary tumor. This is the fourth case of ovarian involvement in which multiple myeloma simulated a Krukenberg tumor; a Krukenberg tumor is a metastatic ovarian tumor that usually occurs following a primary gastrointestinal malignancy.27

**Intracranial Multiple Myeloma**

Traditionally, intracranial plasmacytomas and multiple myeloma include the cranial vault, the skull base only, and the brain parenchyma, originating in the cranial vault or skull base and orbit. Plasmacytomas and multiple myeloma rarely occur in the intracranial area.

An intracranial mass of dural origin, specifically an intracranial plasmacytoma involving the posterior fossa, was diagnosed in a 33-year-old man with a one-year history of multiple myeloma. The patient had begun chemotherapy with capecitabine. The patient was referred by his internal medicine physician to a neurosurgeon because of chronic headache symptoms.

An MR scan indicated a posterior fossa mass. The mass had infiltrated the bone and the intradural and extradural layers. Both masses were removed, and a histopathological study with hybridization/immunofluorescent protein staining confirmed intracranial involvement of multiple myeloma.

This is the only known case of posterior fossa involvement. Including this case, only 25 documented cases of multiple myeloma with dural involvement had been published through 2009. The mean age of patients at diagnosis is 56.2 years, and most are women. The average time lapse before diagnosis of intracranial involvement is 21 months, and 90% die within a month of diagnosis. MR imaging is the modality of choice in nearly all cases of intracranial involvement.

Radiological findings of intracranial multiple myeloma or plasmacytomas can appear as lymphoma, metastasis, sarcoma of the dura mater, osteochondroma, infectious meningitis, or meningioma. When a solitary intracranial mass mimicking menigioma is detected on an MR scan, multiple myeloma should be considered in the differential diagnosis. The origin of the mass and its appearance on an MR scan should be carefully examined before surgery.28

**Pleural Involvement**

Extramedullary multiple myeloma is rare; however, it commonly is found in the nasopharynx, upper respiratory tract, and gastrointestinal tract. Pleural involvement is rarer. In the case of a 40-year-old woman who received a diagnosis of λ light chain multiple myeloma, a pleural mass was found on the woman’s chest radiograph. Her only reported symptom was a fever. A CT-guided fine-needle aspiration from the lesion revealed atypical plasma cells. Aspiration of bone marrow showed 20% abnormal plasma cells, and radiographs of the skull and dorso lumbar spine were absent of lytic lesions. Serum immunofixation electrophoresis revealed a λ light chain. A test for presence of Bence Jones proteins in the patient’s urine later proved to be a false-negative result.

Multiple myeloma with pleural effusions is rare and usually is the result of a concurrent disease process such as amyloidosis. Pleural effusions from malignant myeloma are even less common and are seen in only 1% of multiple myeloma cases.29

**Pleural Effusion Secondary to Pleural Plasmacytoma**

A 66-year-old woman with IgG myeloma was in remission 1.5 years following the initial diagnosis and treatment with chemotherapy when her paraprotein IgG began rising. The patient’s physical symptoms included one week of shortness of breath and right-sided chest pain. A chest radiograph revealed a large right-sided pleural effusion (see Figure 4). A CT-guided pleural biopsy was performed and revealed pleural plasmacytoma, which is not a primary pleural malignancy.

Cytology analysis from the pleural fluid confirmed the presence of plasma cells. The official diagnosis was myelomatous pleural effusion secondary to pleural plasmacytoma. The pleural area was an unusual site for disease recurrence and was the source of an unexplained
rising paraprotein level. A second course of chemotherapy was begun for the patient. Myelomatous pleural effusions can develop from extension of plasmacytomas of the chest wall, invasion of adjacent skeletal lesions, direct pleural involvement by myeloma, or pleural plasmacytoma following lymphatic obstruction secondary to lymph node infiltration.

An IgA paraprotein level is present in up to 80% of cases of pleural effusions. The presence of IgG paraprotein in this case was unusual. Development of pleural plasmacytoma is often a late manifestation of multiple myeloma. Pleural involvement with myeloma cells is aggressive and is associated with a poor prognosis (a mean survival rate of 4 months). Pleural involvement responds poorly to first- or second-line chemotherapy used in traditional multiple myeloma treatment.38

Breast Plasmacytoma
In a 2010 study of 53 German patients with breast plasmacytoma between 1988 and 2010, 85% of breast plasmacytomas were secondary to multiple myeloma; 83% presented with breast lumps; and 8% reported no symptoms. Mammograms displayed round or oval masses in 89% of patients and no abnormalities in 2% of patients. Solitary plasmacytomas comprised 66% of masses, and multiple masses were described in 34% of those with masses, with a mean size of 21 mm (8-90 mm range). Only 9% had breast plasmacytoma as a diffuse infiltration of the breast.

Lesions evaluated on ultrasound were homogeneously echo-poor (dark), hypoechoic, or infrequently mixed hyperechoic-hypoechoic. Primary breast plasmacytoma was associated with a better prognosis than a secondary multiple myeloma manifestation to breast involvement. The authors concluded that breast plasmacytoma is indistinguishable by specific radiological or clinical signs. It easily can be misdiagnosed as primary breast carcinoma or a benign mass. Breast plasmacytoma is recommended for inclusion in the differential diagnosis of patients with multiple myeloma.39

Central Nervous System Presentation
Central nervous system (CNS) multiple myeloma represents only 1% of multiple myeloma cases. An article reviewing clinical and laboratory findings of 109 CNS multiple myeloma patient files was examined from the medical literature. CNS multiple myeloma is defined as the existence of monoclonal plasma cells in the cerebrospinal fluid. Prognosis is extremely poor, with a median survival of 2 months. The mean interval from an initial multiple myeloma diagnosis to a CNS multiple myeloma diagnosis is 18 months.

Only 12% of the total CNS multiple myeloma patients present with no history of multiple myeloma, and at diagnosis of CNS involvement, 20% were in complete remission. The most common clinical symptoms are confusion, limb weakness, and headache, although 16 signs and symptoms can be present. CNS multiple myeloma manifests as localized intraparenchymal lesions, solitary cerebral plasmacytoma, or CNS myelomatosis.32

CNS involvement occurs during all stages of multiple myeloma, but most (almost 80%) of the cases within the patient population subset that was studied were in stage IIIA or IIIB. CT brain scans revealed intracerebral pathology in 21 of the 34 patients. The pathology consisted of hydrocephalus, intracerebral tumors, and osteolytic lesions. CT scans were normal in 12 patients.32

MR scans on 50 patients showed diffuse leptomeningeal involvement in 22 of the 50 patients, localized leptomeningeal involvement in 15, and cerebral masses in 10 of the patients. MR scans were normal in 4 of the 50
patients. Neurological symptoms mainly are caused by hyperviscosity, hypercalcemia, medullary compression, depositions of amyloid, or drug-induced neuropathy. Neurological symptoms are similar to other leptomeningeal malignant neoplasms and include mental status changes, gait disturbances, headache, and cranial nerve palsies. Laboratory results were nonspecific. The most effective treatment regimen is unknown but has included a varied or heterogeneous combination of intrathecal chemotherapy, systemic chemotherapy, or cranial irradiation. Only cranial irradiation alone or in combination with chemotherapy seemed to prolong survival time.

**Thyroid Cartilage Plasma Cell Neoplasm**

A 60-year-old patient presented with hoarseness and a past history of plasmacytoma of the left maxillary sinus without systemic signs of multiple myeloma. Disease recurrence was treated with irradiation, and standard tests for multiple myeloma were conducted. Imaging included noncontrast and postcontrast MR sequences, as well as CT and nuclear bone scans. Serum protein electrophoresis revealed IgGκ. An initial bone marrow biopsy revealed only plasma precursor cells with a slight increase in plasma cells. A bone marrow biopsy performed nearly 5 years later showed a minor amount of abnormal plasma cells considered representative of early development of plasma cell neoplasm. The initial diagnosis was inactive multiple myeloma with a destructive laryngeal lesion.

Skeletal radiographs later revealed multiple lesions throughout the patient’s axial and appendicular skeleton. There are 2 explanations for cartilage involvement: direct cartilage infiltration by adjacent plasmacytoma, or transformation of cartilage to bone with a marrow cavity forming where a plasmacytoma originates. Thyroid cartilage plasma cell neoplasm is considered an extraosseous manifestation of multiple myeloma. Lesions are homogenous, well defined, and enhancing. Before this instance, only 6 cases of thyroid cartilage plasma cell neoplasms had been reported.

**Pancreatic Involvement**

Approximately 25 cases of multiple myeloma involvement in the pancreas have been reported, with most occurring in the pancreatic head. The symptoms are abdominal pain and obstructive jaundice from compression of the common bile duct. A pancreatic plasmacytoma can be difficult to distinguish from a hypervascular neuroendocrine tumor. Percutaneous or open biopsy and endoscopic ultrasound-guided fine-needle aspiration can help rule out other pancreatic masses such as serous and mucinous tumors. MR and CT scanning aid in diagnosis.

**Conclusion**

Multiple myeloma is the most common primary bone disease among adults. The disease involving malignant plasma cells has no known cure. Predominantly affecting people aged 70 years and older, multiple myeloma has been reported in patients aged 20 to 40 years. The incidence of multiple myeloma is expected to increase in the United States as the population ages.

Scientists know that myeloma cells originate from a single B cell that once resided in the lymph node or spleen. Most myeloma cells have an extra chromosome or chromosome trisomy instead of the normal 22 pairs. Nearly 80% of myeloma patients have a high concentration of an abnormal plasma cell that manufactures monoclonal proteins. Myeloma can affect the bones of the axial skeleton, soft tissues, and organs, which interferes with normal body functions and overall health.

An official multiple myeloma diagnosis is made through laboratory tests and a metastatic bone survey. Other imaging modalities, such as CT, 18F-FDG PET-CT, and MR imaging are used to evaluate and monitor the disease and for surveillance of possible relapse. Although prognosis remains poor, outcomes have improved significantly with newer combinations of chemotherapy. Novel biological agents continually are being researched that target myeloma cells and prevent or delay their growth. Some investigators believe a “functional cure” has been achieved with successful autologous stem cell transplants for a subset of low-risk patients.

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References


1. The term *multiple myeloma* was introduced in 1873 to describe:
   a. previously undescribed bone tumors.
   b. the presence of multiple plasma cell sores in bone.
   c. the presence of osteoclasts in blood serum.
   d. a lack of immunity associated with changes in albumin.

2. Which group had the **lowest** incidence of multiple myeloma in the United States from 1975 to 2010?
   a. American Indians/Alaska Natives
   b. blacks
   c. whites
   d. Asian Pacific Islanders

3. Which of the following is a predictor of myeloma?
   a. amyloidosis
   b. plasmacytoma
   c. monoclonal gammopathy of undetermined significance
   d. smoldering myeloma

4. Scientists know that myeloma cells originate from a single B cell that once resided in the lymph node or:
   a. pancreas.
   b. spleen.
   c. liver.
   d. stomach.

5. If a monoclonal protein is present in the blood serum, the number of monoclonal free light chains is too high for the kidneys to absorb, resulting in:
   a. excess red cells in the blood.
   b. excess Bence Jones proteins in the blood.
   c. depletion of white blood cells.
   d. depletion of plasma cells.

6. The most common type of monoclonal protein from myeloma cells is IgG. Which is the second most common?
   a. IgA
   b. IgM
   c. IgD
   d. IgE

*Your answer sheet for this Directed Reading must be received in the ASRT office on or before this date.*
7. Myeloma cells cause osteoclasts to be _______ and accelerate bone loss.
   a. hyperactive
   b. hypoactive
   c. reactive
   d. adaptive

8. According to the article, which of the following is not one of the most important myeloma growth lymphokines?
   a. vascular endothelial growth factor
   b. tumor necrosis factor-alpha
   c. interleukin-7
   d. interleukin-6

9. _______ is a blood transporter of hormones and other small molecules that indicates the overall health of a patient.
   a. Creatinine
   b. Calcium
   c. Albumin
   d. C-reactive protein

10. Multiple myeloma imaging includes structural modalities, including:
    1. radiography.
    2. computed tomography (CT).
    3. magnetic resonance (MR) imaging.
    a. 1 and 2
    b. 1 and 3
    c. 2 and 3
    d. 1, 2, and 3

11. The metastatic bone survey remains in widespread use at baseline and restaging and is relatively sensitive for detecting _______ in the skull and extremities.
    a. focal osteolytic lesions
    b. diffuse osteolysis
    c. multiple plasmacytomas
    d. mild osteopenia

12. A metastatic bone survey is useful for evaluating extramedullary myeloma.
    a. true
    b. false

13. Appearance of a normal hematopoietic marrow on an MR image largely is dependent on a patient’s:
    a. weight.
    b. age.
    c. race.
    d. height.

14. MR imaging is clearly superior to all imaging modalities for an early diagnosis of:
    a. asymptomatic myeloma.
    b. avascular necrosis.
    c. atypical dysplasia.
    d. mild osteopenia.

15. Which of the following can potentially degrade image quality in positron emission tomography (PET)-CT scans?
    a. scar tissue
    b. yellow mucus
    c. brown adipose tissue
    d. white cartilage

16. Patients whose _______ indicates complete remission prior to stem cell transplantation usually have significantly sustained remissions and better survival.
    a. MR exam
    b. ultrasound
    c. metastatic bone survey
    d. PET exam

17. Immediate treatment is not required for _______ myeloma.
    a. symptomatic
    b. smoldering
    c. intramedullary
    d. extramedullary

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18. A complete treatment response requires that a soft tissue plasmacytoma:
   a. never was present.
   b. reduces in size by 50%.
   c. disappears.
   d. remains absent for at least 1 year.

19. Which types of procedures are used to relieve the pain caused by vertebral fractures?
   1. vertebroplasty
   2. kyphoplasty
   3. spinal fusion
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

20. Which of the following was the first chemotherapy drug available to treat multiple myeloma?
   a. lenalidomide
   b. melphalan
   c. thalidomide
   d. bortezomib

21. Allogeneic stem cell transplants are considered riskier than autologous transplants.
   a. true
   b. false

22. Genetically engineered erythropoietin is part of an ancillary therapy aimed at improving problems associated with:
   a. treatment-related nausea.
   b. chronic anemia.
   c. bone density.
   d. stem cell rejection.

23. Multiple myeloma with ________ involvement can simulate a Krukenberg tumor.
   a. breast
   b. pleural
   c. ovarian
   d. central nervous system

24. Which of the following statements is true regarding intracranial involvement of multiple myeloma?
   a. Dural involvement is common; more than 250 cases are documented each year.
   b. The mean age of patients who have dural involvement at diagnosis is 36.2 years.
   c. Intracranial involvement is rare but relatively benign; only 20% of those with dural involvement die within a month of diagnosis.
   d. There is only 1 reported case of posterior fossa involvement.

25. Central nervous system multiple myeloma is defined as the presence of monoclonal plasma cells in the:
   a. cerebrospinal fluid.
   b. vertebral bodies.
   c. skull bone.
   d. meninges.