NORMAL BONE MARROW ANATOMY AND PHYSIOLOGY

The basic microstructure of bone marrow consists of an osseous framework housing fat cells and hematopoietic cells both supported by a system of reticulum cells, nerves, and vascular sinusoids (Davis and Trubowitz, 1982). The trabecular or cancellous bone is composed of primary and bridging secondary trabeculae. By volume, this osseous tissue occupies 15% of the bone cavity and provides both architectural support and a mineral depot (Politis et al., 1983). Cellular constituents of marrow occupy the remaining 85%. These constituents include all stages of erythrocytic and leukocytic development and fat cells and reticulum cells. Erythroid, granulocytic, and megakaryocytic cell lines replenish the body's supply of red cells, white cells, and platelets (Volger III and Murphy, 2006).

Bone marrow is categorized into two types of tissue based on differences in their color at gross pathologic examination. The active, hematopoietic component is comprised mostly of erythrocytes and their precursors and is denoted as “red” marrow, whereas “yellow” (inactive) marrow is comprised primarily of fat (Barr and Anderson, 2002).

Important anatomic and compositional differences exist between these two types of marrow. On average, the chemical composition of red marrow is approximately 40% water, 40% fat, and 20% protein. The cellular composition of red marrow is 60% hematopoietic cells and 40% fat cells. Red marrow has a rich arborized vascular network. Yellow marrow's chemical composition is approximately 15% water, 80% fat, and 5% protein. Its cellular composition is 95% fat cells and 5% nonfat cells. Physiologically, the fat cells in yellow marrow are relatively stable,
whereas those in red marrow appear to be labile. Yellow marrow has a sparse vascular network (Volger III and Murphy, 2006).

**Marrow Conversion:**

The amount and distribution of red and yellow marrow change with age. This normal conversion from red to yellow marrow occurs in a predictable and progressive manner and is completed by an individual's middle 20s (Kaplan et al, 2001).

At birth, virtually the entire marrow space contains red marrow. During growth and development, conversion of red to yellow marrow occurs throughout the skeleton. This is a normal physiologic process and has a predictable and orderly pattern. This conversion begins in the immediate postnatal period and is first evident in the terminal phalanges of the hands and feet. Although generally symmetric, the rate and extent of conversion is not uniform but varies according to site in a particular bone and among bones (Volger III and Murphy, 2006).

Conversion from red to yellow marrow proceeds from the extremities to the axial skeleton, occurring in the distal bones of the extremities (feet and hands) first, and progressing finally to the proximal bones (humeri and femora). This process occurs in a roughly symmetric manner on each side in a given individual. Progression of conversion from red to yellow marrow within individual long bones occurs in the following sequence: epiphyses and apophyses first, then the diaphysis, followed by the distal metaphysis and finally the proximal metaphysis. Conversion also occurs in centripetal fashion within a bone, with fat predominating centrally, whereas red marrow predominates at the outer margins or periphery (subcortical region) of the medullary space of flat bones, long bones and vertebral bodies (Figure 1) (Kaplan et al, 2001).

Epiphyses and apophyses must be considered independently. These structures lack marrow until they begin to ossify. What remains unclear is
how much red marrow appears at these sites and how long it persists. Undoubtedly, any red marrow contained in these structures undergoes rapid, although not necessarily complete, conversion to yellow marrow. The conversion begins in the central marrow cavity and progresses toward the subchondral or peripheral subcortical bone. Thus, as a general rule, epiphyseal and apophyseal ossification centers can be thought of as containing yellow marrow from very early in growth and development. Yellow marrow persists in epiphyses and apophyses throughout life with the proximal femoral and proximal humeral epiphyses/apophyses being limited exceptions to this rule. Other exceptions may exist; however, to date, they remain unidentified (Volger III and Murphy, 2006). Kaplan et al, 2001 postulated that when epiphyses and apophyses ossify, they have red marrow within them only transiently, for a matter of a few weeks, before conversion to yellow marrow occurs.

Usually by 25 years of age, the process of primary red marrow conversion to yellow marrow is complete and a balanced distribution of red and yellow marrow has been achieved (Figure 2) (Mitchel et al, 1986). This balance will vary from person to person as it is influenced by at least age, gender, and health. Similarly, the balance between red and yellow marrow achieved in individual bones varies by location. Red marrow is predominately concentrated in the axial skeleton (skull, vertebrae, ribs, sternum, and pelvis) and the proximal appendicular skeleton (proximal femora and humeri). Yellow marrow dominates the remaining portion of the appendicular skeleton and is variably admixed throughout the axial skeleton. (Vande Berg et al, 1997a).

Factors modulating this conversion of red to yellow marrow are largely unknown. However, temperature, vascularity and low oxygen tension have been implicated (Volger III and Murphy, 2006).
Reconversion of yellow to red marrow

Reconversion of yellow to red marrow occurs in areas where sinusoidal networks and perivascular reticular cells can appear rapidly: metaphyseal and metaphyseal equivalent regions, subchondral epiphyseal areas, and diaphyseal endosteal spaces. This pattern is the reverse of red to yellow conversion in that reconversion to red marrow begins in the ends of the bones and progresses toward the mid-diaphyses (Barr and Anderson, 2002).

The process of red to yellow marrow conversion is, at times, halted or reversed as alterations in the body's demand for hematopoiesis provoke a "reconversion" of yellow marrow to red marrow. During this reconversion, yellow marrow is transformed to red marrow throughout the skeleton in the reverse sequence of the primary red to yellow marrow conversion described above. Thus, the process occurs first in the axial skeleton followed by the appendicular skeleton in a proximal to distal sequence. Within individual bones, reconversion is first seen at endosteal locations in metaphyses or epiphyses or their equivalents. From there it progresses toward the central marrow space and toward the diaphyseal subcortical bone, ultimately extending into the central diaphyseal marrow cavity. Temperature, low oxygen tension, and elevated erythropoietin are again implicated in initiating and modulating this process, although the actual mechanisms and controlling factors remain largely unknown (Volger III and Murphy, 2006).
Figure (1): Age-related changes in red/yellow marrow distribution. The natural conversion of red to yellow marrow is illustrated by drawing of the right lower extremity at 7-year intervals. At birth, virtually the entire ossified skeleton contains red marrow. Conversion of red to yellow marrow begins shortly after birth and is first evident in the distal appendicular skeleton (hands and feet). Through the ongoing years, the process gradually progresses from distal to proximal with respect to the skeleton as a whole and from diaphyseal to epiphyseal in individual long bone (From Kricun; 1985).

Figure (2): Adult pattern of red/yellow marrow. Usually by 25 years of age, the primary conversion of red to yellow marrow has been accomplished and the adult distribution of red/yellow marrow established. Red marrow is concentrated in the axial and proximal appendicular skeleton, whereas yellow marrow occupies the remainder of the appendicular skeleton. (From Kricun; 1985).
TECHNIQUES OF MR IMAGING OF BONE MARROW

In the MR evaluation of bone marrow and bone marrow disorders, the major technical considerations to be addressed are pulse sequences, slice parameters, imaging planes, contrast agents, and types of coils to be used. The MR appearance of bone marrow varies greatly between pulse sequences. Numerous pulse sequences have been and continue to be developed, each sequence aimed at improving some aspect of MRI (Volger III and Murphy, 2006).

Spin echo imaging (Figures 3-9):

Spin-echo pulse sequences (both conventional and fast) with T1- and T2-weighted images have traditionally been the method used in MRI of marrow, and as such, much of the current knowledge about normal and abnormal bone marrow is based on these types of imaging. TRs used in obtaining T1 and T2 weighted images do not need to be absolute but can vary depending on the anatomic region to be covered. Larger anatomic areas require longer repetition times. As a general guideline, however, the TR for a T1-weighted sequence should be kept below 700 ms and the TR for a T2-weighted sequence should exceed 2,000 ms. (Volger III and Murphy, 2006).

Accepted echo delays for T1-weighted images are less variable, generally less than 30 ms and preferably 20 ms. To achieve adequate T2-weighting, TEs of 80 ms or greater are necessary. Thus, using these guidelines, a routine MR evaluation of bone marrow might include T1-weighted images using a TR of 500 ms and TE of 20 ms and T2-weighted images obtained with a TR of 2,000 ms and a TE of 80 ms. Studies obtained in this manner take advantage of many inherent marrow properties (Volger III and Murphy, 2006).

On the T1-weighted images, contrast is predominately a function of T1 relaxation time. Because of the short T1 of lipid, the signal from fatty
marrow is optimized. Tissues containing lesser amounts of fat or having longer T1 relaxation times become conspicuous against the background of high-signal fatty marrow. Thus, bone, red marrow, muscle, and most pathologic processes can be readily identified. T1-weighted images also provide excellent anatomic detail (Figures 3, 4, 5&6) (Volger III and Murphy, 2006).

With T2-weighting, the signal intensity of red marrow slowly increases, whereas that of yellow marrow slowly declines, making it more difficult to discriminate between the two. Because many pathologic processes have very long T2 relaxation times (greatly exceeding those of red and yellow marrow), they are conspicuous in the marrow. Narrowing the T2 contrast difference between a pathologic process and normal marrow makes the pathologic process less conspicuous. Adding fat saturation to T2-weighted images significantly increases lesion detection and should be incorporated into bone marrow MR studies when available (Volger III and Murphy, 2006).

**Short time inversion recovery (STIR) (Figures 8 &10):**

Fat suppression is used in routine magnetic resonance (MR) imaging for many purposes, but two main indications can be identified. First, fat suppression is used to suppress the signal from normal adipose tissue to reduce chemical shift artifact or improve visualization of uptake of contrast material. The second main use is tissue characterization, particularly in adrenal gland tumors, bone marrow infiltration, fatty tumors, and steatosis (Delfaut et al; 1999)

In inversion-recovery imaging, suppression of the fat signal is based on differences in the T1 of the tissues. The T1 of adipose tissue is shorter than the T1 of water. After a 180° inversion pulse, the longitudinal magnetization of adipose tissue will recover faster than that of water. If a 90° pulse is applied at the null point of adipose tissue,
adipose tissue will produce no signal whereas water will still produce a signal. Therefore, the fat signal can be suppressed by using a short TI inversion-recovery (STIR) sequence (Delfaut et al; 1999).

In STIR imaging, the signal from fat is nulled, making it appear dark on the images. Tissues having T1 or T2 relaxation values that differ from fat will have greater signal intensity than fat. In fact, because of the nature of inversion recovery sequences, T1 and T2 values are additive, making STIR imaging perhaps the most sensitive of all pulse sequences for detecting marrow abnormalities (Volger III and Murphy, 2006).

The following findings are characteristic of STIR images:
- Fat is black.
- Combinations of red and yellow marrow are light gray (i.e., intermediate).
- Most marrow tumors are bright white.
- Although red marrow demonstrates increased signal intensity on STIR images, most pathologic conditions involving marrow replacement or infiltration generate greater signal intensities. Fibrous tissue, calcification, and hemosiderin deposits are low in signal intensity, whereas fluid, edema, or recent hemorrhage is bright. Muscle remains intermediate in signal intensity (Bredella and Stoller, 2007).

The fast spin-echo STIR technique decreases imaging time significantly and produces diagnostic accuracy comparable to that of conventional STIR sequences. Both fat-suppressed T2-weighted fast spin-echo and fast spin-echo STIR sequences used in conjunction with T1-weighted images represent the key imaging protocols for optimizing marrow tissue contrast (Bredella and Stoller, 2007).

However, the most misleading disadvantage of STIR imaging is that the fat suppression is nonspecific. Signal from tissue or fluid with a T1 similar to that of fat will also be suppressed. Examples of such tissue
or fluid are mucoid tissue, hemorrhage, proteinaceous fluid, and gadolinium or melanin in a given concentration. Conversely, areas of fatty infiltration or tumors containing fat might not have the same T1 as white fat (*Delfaut et al; 1999*).

**Gradient-echo pulse sequences:**

Gradient-echo recall techniques have become increasingly popular, primarily because of their ability to increase the rate of data acquisition and decrease scan times (*Bredella and Stoller, 2007*).

Advantages of gradient-echo techniques include: Effective T2 weighting, High resolution and adequate signal-to-noise ratio without the need for interslice spacing. These advantages make this a useful complement to T1 spin-echo imaging (*Bredella and Stoller, 2007*).

The following findings are characteristic on gradient-echo recall images:

- Red marrow does not demonstrate increased signal intensity on gradient-echo images and may be difficult to differentiate from fatty marrow.
- A high proportion of trabecular bone in areas such as the epiphysis may further modify gradient-echo contrast resulting in decreased signal intensity in these areas (*Bredella and Stoller, 2007*).

Gradient-echo pulse sequences provide an alternative to STIR and T2-weighted spin-echo sequences yet at much shorter scan times. Numerous gradient-echo sequences exist [gradient recalled steady state (GRASS), fast low-angle single-shot imaging (FLASH), fast imaging with steady state free precession (FISP), etc.]. All are based on the generation of a gradient echo rather than the classic 180° refocusing pulse used in spin-echo pulse sequences. The flip angle (theta) can be kept small in gradient-echo pulse sequences, enabling substantial reduction in imaging time. (*Volger III and Murphy, 2006*).
Figure (3): Sagittal T1-WI of the ankle of a 2-year-old boy. Bone marrow has a high signal intensity suggestive of yellow marrow. Only the distal tibial metaphysis shows intermediate signal intensity compatible with residual red marrow. *(From Vande Berg et al; 1998).*

Figure (4): Sagittal T1-WI of the lumbar spine in a 24-year-old female demonstrating fat conversion of red marrow around the central vertebral veins (arrows). *(From Vande Berg et al; 1998).*

Figure (5): Sagittal T1-WI of the sacrum and coxycx of a 27-year-old male shows the predominant centripetal vector of bone marrow conversion with a higher fatty content in the caudal than in the cranial aspect of the spine. *(From Vande Berg et al; 1998).*

Figure (6): Coronal T1-WI of the knee of a 47-year-old female with benign hematopoietic marrow hyperplasia. Confluent areas of intermediate signal intensity are depicted in the distal femoral metaphysis. The distal femoral epiphysis and proximal tibia are uninvolved. *(From Vande Berg et al; 1998).*
Chemical shift imaging:

The chemical shift phenomenon refers to the signal intensity alterations seen in magnetic resonance (MR) imaging that result from the inherent differences in the resonant frequencies of precessing protons. Chemical shift was first recognized as a misregistration artifact of image data. More recently, however, chemical shift has been recognized as a useful diagnostic tool. (Hood et al; 1999).

Chemical-shift imaging is used to produce images that emphasize either the water or fat component of marrow by temporal separation of their respective returning MR signals. Red and yellow marrow differentiation is thus possible on T1-weighted images. Differences in resonant frequencies of fat and water protons (3.5 ppm or 75–150 Hz) allow for temporal dephasing after RF pulse excitation. This property is used to develop water and fat images by emphasizing in-phase or out-of-phase tissue properties, thus suppressing fat or water signal (Bredella and Stoller, 2007).

Chemical shift imaging improves lesion detection and red/yellow marrow discrimination on spin-echo and gradient-echo sequences. Using chemical shift techniques, fat and water molecules present in the same voxel will cancel, producing no net signal in the respective pixel. Thus, when tissues containing excess water (most pathologic processes) occur in fatty marrow, a dark interface appears, making that tissue more conspicuous. Red marrow, due to its higher water content, is also more conspicuous. Some chemical shift sequences allow selective fat or water images. Use of these sequences shows initial promise in predicting whether bone marrow signal abnormalities result from neoplastic or non-neoplastic causes (Volger III and Murphy, 2006).
Whole-Body MR Imaging (Figure 10):

Whole-body fast MR imaging protocols have recently been shown to be an effective and time-efficient means of evaluating the entire skeleton for metastases, multiple myeloma, and staging of head and neck cancers and lymphoma (Goo et al., 2005, Herborn et al., 2005 and Schmidt et al., 2005). Studies comparing whole-body STIR MR imaging with bone scintigraphy in patients with suspected metastatic disease have shown that MR imaging is more sensitive than bone scintigraphy in lesion detection (Eustace et al., 1997 and Steinborn et al., 1999).

Using fast MR sequences, whole-body MR imaging has been shown to be superior to bone scan in detecting lesions in the extremities, pelvis, and spine and provides additional important information about tumor morphology, tumor extension, and neurologic complications. Whole-body MR imaging is also used to detect response to therapy. Recent protocols have been shown to significantly decrease acquisition times, and most adults may be completely imaged from head to toe using a standard body coil. In comparing whole-body MR imaging using a rolling table platform with bone scintigraphy, excellent correlation between the two modalities in lesion detection has been demonstrated, and the examination time was 40 minutes or less (Bredella and Stoller 2007).

$^1$H (Proton) MR spectroscopy:

In vivo proton MR spectroscopy is already an established technique for brain tumors and breast and prostate cancer. Novel applications of MR spectroscopy in the evaluation of other malignancies such as cervical cancer and soft-tissue and neck tumors have also shown promising results. Proton MR Spectroscopy of bone tumors has received little attention. Recent literature suggests encouraging results of in vivo proton MR spectroscopy in differentiating benign from malignant
musculoskeletal tumors (*Sah, et al; 2008*)

*Fayad et al; 2007* also stated that Proton MR spectroscopy has been used extensively to investigate tumor metabolism in other organ systems but has been used in the characterization of musculoskeletal lesions in a limited fashion, with only three published studies to date.

A diverse group of pathologic conditions, including benign and malignant bone and soft-tissue tumors and nonneoplastic lesions, are evaluated. This precluded any specific conclusion regarding the spectroscopic finding of any particular disease entity, and the need for further studies focusing on a specific disease in a larger group of patients is recognized. MR spectroscopy detection of elevated choline is reported to be 95% sensitive in differentiating benign from malignant musculoskeletal tumors. However, the specificity is relatively less because few hypercellular benign tumors reveal an elevated choline peak (*Sah, et al; 2008*).

**Other Techniques:**

Techniques aimed at quantifying bone marrow cellularity have been identified, including chemical shift misregistration and parametric MRI (*Ishizake et al; 1995 and Ballon et al; 1998*). These techniques show good correlation with histomorphometric data in small numbers of patients and may potentially be beneficial in monitoring some marrow disorders. Currently, however, these methods have not been validated in large clinical studies, and their future role remains unclear (*Volger III and Murphy, 2006*).
**Gadolinium-enhanced MR imaging of bone marrow:**

To date, MR contrast agents (e.g., gadolinium) have not developed a defined utility in evaluation of diffuse marrow disease. These agents hold promise for demonstration of marrow involvement by neoplastic processes in certain settings and may improve the specificity of MR for separation of benign from malignant disorders. At present though, routine use of these agents for evaluation of diffuse marrow disorders is not required (*Volger III and Murphy, 2006*).

**Surface coil, slice thickness, and interslice gap:**

Size of the anatomic region to be evaluated influences many MR scanning parameters, including surface coil selection, slice thickness, and interslice gap. Smaller anatomic regions may be better imaged with surface coils, whereas larger regions require body coils. Comparison with the contralateral extremity is generally desirable, necessitating use of a body coil. Slice thicknesses on the order of 3 to 5 mm with no interslice gap usually provide the resolution necessary in small anatomic areas. However, 5-mm slices with 5-to 10-mm gaps are often needed to cover larger regions. (*Volger III and Murphy, 2006*).

**Magnetic Resonance Survey Evaluation:**

The protocol for an MR survey examination for marrow evaluation uses T1-weighted coronal images of the pelvis and proximal femurs, which are adult sites of red marrow concentration. These images are acquired with large (40 cm) fields of view to include assessment of lumbosacral spine marrow. Coronal STIR images are obtained to null fat signal and identify abnormal T1 or T2 prolongation. Fat-suppressed T2-weighted fast spin-echo sequences may be used when thin slice or multiplanar imaging is required in a limited period of time (*Bredella and Stoller 2007*).
Figure (7): Normal appearance of spinal bone marrow in a 45-year-old woman: T1-weighted (A) and T2-weighted, fat-suppressed fast spin echo (B) sagittal MR images of the lumbar spine. Note increased signal of the vertebral bodies, relative to the intervertebral discs in (A) and increased deposition of fatty marrow around the basivertebral veins (arrowheads). On the T2-weighted image, normal intervertebral discs are brighter than the vertebral bodies; low signal in the L4-L5 and L5-S1 discs is due to degenerative changes (arrows). (From Moulopoulos and Dimopoulos; 1997).

Figure (8): (A) Coronal T1-weighted image shows normal yellow marrow of the proximal femurs (black arrows). Residual red marrow in the femoral metaphyses is of intermediate signal (white arrows). (B) Yellow marrow is dark on the corresponding coronal STIR image (arrows). Areas of red marrow demonstrate higher signal intensity than areas of yellow marrow (arrowheads). (From Bredella and Stoller; 2007).
Figure (9): (A) Residual metaphyseal red marrow is seen as patchy regions of low signal intensity (black arrows) on a T1-weighted coronal image. (B) The red marrow is hyperintense on the corresponding fat-suppressed T2-weighted fast spin-echo image (white arrows). (From Bredella and Stoller; 2007).

Figure (10): Whole-body MR imaging using coronal T1-weighted (A) and coronal STIR (B) sequences. Whole-body MRI is a sensitive and fast technique for evaluating the entire skeleton for abnormalities. (From Bredella and Stoller; 2007).
OTHER IMAGING MODALITIES OF BONE MARROW

Conventional Radiography:

Traditionally, conventional radiography is the initial examination obtained when a bone marrow process is suspected. These images provide an overview of the osseous pattern and may be diagnostic when specific features are present. The limitations of plain radiographs are well recognized, particularly with respect to sensitivity, in that considerable loss of trabecular bone is required before a marrow abnormality becomes radiographically evident. Thus, though well suited as an inexpensive survey, radiography often does not provide sufficiently detailed anatomic and physiologic information. Much of this information is now obtained by other imaging methods (Volger III and Murphy, 1988).

In myeloma bone disease, Skeletal radiography continues to be the primary diagnostic study to aid in detection of destructive bone changes in MM. Estimates suggest that approximately 50% of bone destruction must occur before there is radiographic demonstration of the abnormality and that 75% of patients with MM will have positive radiographic findings (Lecouvet et al., 2001).

Multiple myeloma may present in a variety of radiographic patterns. Particularly in the spine, it may be seen only as diffuse osteoporosis with no clearly identifiable lesion; multiple compression fractures of the vertebral bodies may also be evident. More commonly, it exhibits multiple lytic lesions scattered throughout the skeleton. In the skull, characteristic “punched-out” areas of bone destruction, usually of uniform size, are noted, whereas the ribs may contain lace-like areas of bone destruction and small osteolytic lesions, sometimes accompanied by adjacent soft-tissue masses. Areas of medullary bone destruction are noted in the flat and long bones, and if these appear about the cortex, they are accompanied by scalloping of the inner cortical margin. Ordinarily,
there is no evidence of sclerosis and no periosteal reaction. Fewer than
1% of myelomas may be of a sclerosing type called sclerosing
myelomatosis (Greenspan, 2004).

In plasmacytoma, the lesion is destructive, sclerosis being rare. The
margin is often well-defined. Cortical thinning with expansion is usually
present and apparent trabeculation or a ‘soap bubble’ appearance is
common. The cortex is thinned out to an eggshell thickness, but not
destroyed completely, although it frequently produces a visible soft-tissue
mass. The sites affected usually contain persistent red marrow—the axial
skeleton, pelvis, proximal femora, proximal humeri, and ribs. Peripheral
lesions are rare. Involvement of a vertebral body is common, sometimes
leading to early collapse. Sometimes a whole vertebral body is lost, with
geographical destruction of the cortices of the adjoining bodies, usually
posteriorly. Extension across the disc space is a rare feature. In long and
flat bones, plasmacytoma may resemble an aneurysmal bone cyst or an
expanding metastasis (Stoker and Saifuddin, 2001).

In leukemia, overproduction of leukaemic cells causes destruction
of the trabeculae of the medulla and the endosteal cortex. Further
proliferation leads to extraosseous spread. The bone changes in children
are: metaphyseal lucencies, diffuse destruction of bone, osteolytic lesions,
osteoblastic lesions, mixed lesions and periosteal reaction. Metaphyseal
lesions are common and may occur early. The metaphyseal lucent bands
primarily affect the sites of maximum growth, e.g. distal femur, proximal
tibia and distal radius, but other metaphyses and the vertebral bodies are
affected later. Diffuse destruction of bone is more extensive trabecular
destruction in the medulla. The cortex becomes eroded on its endosteal
surface and may be destroyed. Osteopenia may result in vertebral
collapse. Osteolytic lesions are particularly involve the diaphyses of long
bones and are also observed in adults. Even in children, such lesions are
present in over 60% of patients with skeletal leukaemic involvement. Osteoblastic lesions are rare and its cause is unknown. Sclerotic changes in the metaphyses of children may occur spontaneously or as a result of therapy. Mixed lesions are rarer than the common lytic lesions but more common than blastic lesions. Periosteal reaction is often due to proliferation of leukaemic deposits deep to the periosteum. Subperiosteal haemorrhage may occur and produce a similar radiological appearance. Cortical destruction may involve the medial aspect of the proximal humerus, tibia and sometimes femur. This is not specific and may be found in children with other disseminated malignancies, particularly neuroblastoma. (Stoker and Saifuddin, 2001).

In Hodgkin disease, only about one third of skeletal lesions are solitary, and scintigraphy is mandatory to identify further lesions. Lesions may be lytic, sclerotic or mixed. Osteolytic lesions or mixed lesions account for almost 90% of cases, the remainder being purely sclerotic. All types may occur in the same patient and the degree of sclerosis may vary. In Spine, HD most commonly causes sclerosis, causing ‘ivory’ vertebral body. Vertebral collapse takes place early with lytic lesions. The disc spaces are usually preserved. Preservation of the cortex of the vertebral end plate is a feature favouring HD. Marginal erosion of the anterior border of one or more vertebral bodies is also found occasionally, possibly by direct spread from affected nodes. Periosteal reaction without other bone change can also be caused by involvement of the paravertebral nodes. In the thoracic region, paravertebral masses may precede radiographic or scintigraphic evidence of bony involvement. Rib lesions are common. Multiple lytic lesions predominate and may be associated with soft-tissue masses. Occasionally the ribs appear expanded (Stoker and Saifuddin, 2001).
The radiographic appearance of primary bone lymphoma is variable and nonspecific. Three radiographic patterns of primary bone lymphoma were identified. The lytic-destructive pattern is the most common radiographic appearance of primary bone lymphoma, it may be permeative or moth-eaten. Occasionally, the lesion may manifest with focal lytic areas with well-defined margins. Cortical breakthrough, pathologic fractures and soft-tissue masses represent a more aggressive pattern of involvement and a poorer prognosis. Periosteal reaction may be either lamellated or layered (onion-peel appearance), or broken. Blastic-Sclerotic Pattern is rare in primary bone lymphoma compared with metastatic bone lymphoma. However, a mixed lytic lesion with sclerotic areas can be seen. Hodgkin disease of bone (the less common subtype of primary bone lymphoma) tends to be sclerotic but lytic lesions predominate. Sclerotic areas can, however, develop in an originally lytic pattern after therapy (irradiation and chemotherapy). Subtle or "Near-Normal" Findings, A third pattern seen and described in primary bone lymphoma is the near absence of detectable abnormalities on plain radiographs (Krishnan et al., 2003).

In Ewing sarcoma, The radiographic presentation of this malignancy is usually rather characteristic; the lesion is poorly defined, marked by a permeative or moth-eaten type of bone destruction, and associated with an aggressive periosteal response that has an onionskin (or “onion peel”) or, less commonly, a “sunburst” appearance, and a large soft-tissue mass. Occasionally, the bone lesion itself is almost imperceptible, with the soft-tissue mass being the only prominent radiographic finding (Greenspan, 2004).

**Scintigraphy:**

Whereas conventional radiography provides an anatomic survey of the osseous superstructure, scintigraphy can be looked on as providing a
physiologic survey of either marrow elements themselves or the surrounding osseous elements. In general, radionuclide evaluation of bone marrow can be accomplished either directly or indirectly. Direct methods include physiologic assessment of either hematopoiesis or phagocytosis. In the evaluation of hematopoiesis, active erythroid precursors are targeted and erythropoetic marrow is imaged. The parameter assessed is incorporation of a transferrin-bound isotope, the prototype tracer of which is radiolabeled iron (Volger III and Murphy, 1988).

To assess phagocytosis, phagocytic cells of the reticuloendothelial system are targeted and imaged. The particular parameter assessed is the removal of a radioactive colloid from the bloodstream, and the prototype tracer is technetium-99m sulphur colloid. Although erythroid and reticuloendothelial elements can be independently assessed, in general, these two bone marrow elements will have similar distributions. In other words, the distribution of one generally reflects the distribution of the other. This also holds true for most disease processes, with the rare exception of those that result in ineffective erythropoiesis. In these circumstances, just the reticuloendothelial elements expand (Volger III and Murphy, 1988).

Whereas direct methods of bone marrow evaluation focus on imaging either erythroid or phagocytic elements of red marrow, indirect methods focus on total marrow content, regardless of its components. The parameter assessed in this type of imaging is bone remodeling (a balance of blood flow and metabolism) in response to a physiologic alteration, and the prototype tracer is Tc-99m diphosphonate. This is perhaps the most commonly ordered radionuclide study for assessment of bone marrow disease. As such, the advantages and limitations of this study are well known. Scintigraphy certainly provides a sensitive physiologic
sunvey of the entire skeleton. Lack of anatomic detail and low specificity are generally recognized as its shortcomings (Volger III and Murphy, 1988).

Wakasugi et al., 2002 evaluated the potential of $^{99m}$Tc-hexakis-2-methoxyisobutylisonitrile (MIBI) for detecting bone metastases in comparison with a conventional bone tracer $^{99m}$Tc-hydroxymethylene diphosphonate (HMDP) scans. Their study shows that $^{99m}$Tc-MIBI scans can detect bone metastases with better sensitivity than conventional $^{99m}$Tc-HMDP bone scans. In addition, $^{99m}$Tc-MIBI detects few abnormalities in lesions with skeletal trauma, degenerative disease, and many other benign active disorders of the bones and joints. $^{99m}$Tc-MIBI scans showed significantly higher sensitivity for detecting metastases, especially in the femur and humerus, than $^{99m}$Tc-HMDP scans. In some patients, $^{99m}$Tc-HMDP scans did not detect any metastatic lesions, but $^{99m}$Tc-MIBI scans correctly detected bone metastases.

$^{67}$Ga scintigraphy has a high sensitivity and specificity for the diagnosis of bone lymphoma. $^{67}$Ga scintigraphy is a better predictor of the long-term outcome of patients with lymphoma of the skeleton than are anatomic imaging modalities such as CT. Tailoring and optimization of treatment in patients with bone lymphoma based on functional data provided by nuclear medicine procedures should increase the rate of successful therapy and decrease treatment-related toxicity (Israel et al., 2002).

**Computed Tomography:**

In computed tomography (CT), the image of normal marrow consists of a combination of fatty marrow, hematopoietic marrow, and intramedullary cancellous bone. As a result of the variable normal distribution of both yellow and red marrow, CT images of marrow from different regions within a bone may have different appearances. For
example, in long bones such as the femur, due to the predominance of yellow marrow in the diaphyseal region, CT images at this level show low-density marrow. When measured, the marrow has predominantly negative Hounsfield values on the order of -100 HU (Helms et al., 1981).

Hounsfield values vary throughout the long bones due to differing combinations of red marrow, yellow marrow, and cancellous bone at each level. Thus, absolute Hounsfield values are location dependent. Diagnostic limitations imposed by this variability can be overcome by comparison with the patient’s opposite side. It is established that Hounsfield values at similar diaphyseal locations in long bones are generally comparable such that a difference of 20 HU between sides would be considered beyond the 95% confidence limits and thus abnormal (Datz and Taylor, 1985).

In contrast to those of diaphyseal marrow, Hounsfield values in the metaphyseal and epiphyseal regions are generally positive, sometimes approaching 100 HU. Again, the values are location dependent and change more dramatically between CT sections than in the diaphyseal region. This probably relates to greater variations of hematopoietic marrow and amounts of trabecular bone. Perfectly symmetric positioning, then, becomes crucial in order to obtain reliable numbers from the contralateral side for comparison. Given accurate positioning, however, Hounsfield readings from the two sides should be similar. If they are found to differ by greater than 20 HU, this is also considered abnormal (Helms et al., 1981).

A positive Hounsfield value greater than 15 HU indicates abnormal marrow. Ct also show calcification, subtle cortical and periosteal changes (Hermann et al., 1984).

One of the well-recognized advantages of CT is the anatomic detail that the method provides. These capabilities allow excellent definition of
trabecular bone and some degree of separation of yellow and red marrow. Precise definition of yellow and red marrow with CT, however, has not been proved. The protocol for a particular CT study will depend on the specific disease process and anatomic site undergoing evaluation (Volger III and Murphy, 1988).
MR APPEARANCE OF NORMAL BONE MARROW

**Principles of MRI of the bone marrow:**

Human bone marrow has two characteristics: First, yellow marrow contains a large number of fat protons and red marrow a significant amount of water protons, MRI offers the opportunity to map the distribution of red and yellow marrow. Second, the balance between fat and nonfat components of the bone marrow is altered with aging and under various abnormal conditions. Conversion of red to yellow marrow is a physiological process that explains age-related changes in red marrow distribution and composition, which in turn dictate the distribution of most marrow lesions (*Vande Berg et al, 1998a*).

**Basic contributors to bone marrow MR appearance:**

Fat, water, protein, and mineral are the basic constituents of bone marrow that contribute to the formation of its MR image. As relative amounts of these constituents change, the signal intensity of marrow is altered accordingly (*Volger and Murphy, 1988*).

**Fat:**

Fat cells are responsible for the greatest fraction of marrow signal on T1-weighted images. Most protons in fat are contained in hydrophobic CH2 groups and demonstrate very efficient spin-lattice relaxation resulting in a particularly short T1 relaxation time and thus high signal intensity on T1-weighted spin-echo images. Spin-spin relaxation of fat is less efficient, resulting in some prolongation of its T2 relaxation time and thus moderate signal intensity on T2-weighted spin-echo images (*Volger III and Murphy, 2006*).

**Water:**

Water in tissue is thought to exist in different forms. Tissues rich in free water (extracellular water) show longer T1 and T2 relaxation times,
whereas those having greater amounts of bound (intracellular) water demonstrate a shortening of T1 and T2 relaxation values (Mitchell et al, 1987). The relative contribution of each type of water to overall marrow signal is not clearly defined. Nevertheless, as the amount of marrow water increases, it is logical to expect lower signal intensity on T1-weighted images and higher signal intensity on T2-weighted images (Volger III and Murphy, 2006).

**Protein:**

The contribution of protein to marrow signal intensity is poorly understood. Protein in general has a long T1 relaxation time due to the large size of the molecules (Mitchell et al, 1987). Yet, protein in solution will result in a shortening of the T1 relaxation time of that solution. The individual contribution of these competing signal patterns to overall marrow signal intensity remains unclear (Volger III and Murphy, 2006).

**Mineral:**

Mineral contributes in a negative fashion to bone marrow signal intensity through two different mechanisms. First, because of a lack of mobile protons, the mineral matrix produces little or no signal. Second, inhomogeneous susceptibility where mineral matrix interfaces with water or fat results in local field gradients and signal loss. The mineral matrix of bone marrow is contained in trabecular bone. Because metaphyses and epiphyses contain greater amounts of trabecular bone, signal intensity at these sites is altered accordingly (Volger III and Murphy, 2006).

**Red and yellow marrow signal intensity:**

Yellow marrow, because of its high fat chemical composition (80%), displays signal intensity comparable with that of subcutaneous fat on T1- and T2-weighted images. For comparison purposes, yellow marrow is higher in signal intensity than muscle on both pulse sequences. Red marrow having larger fractions of water (40%) and protein (40%)
with a smaller fraction of fat (20%), displays signal intensity lower than that of yellow marrow on T1-weighted images. As a reference, red marrow signal intensity is generally slightly greater than normal muscle or nondegenerated intervertebral discs on T1-weighted images (Carroll et al, 1997). The only exception to this rule occurs in infants. At birth, red marrow contains very little fat. As a result, red marrow signal intensity on T1-weighted images will be lower than that of muscle or inter-vertebral disc until approximately 2 months of age (Sebag et al, 1993).

As cellularity of the red marrow decreases, its T1 signal intensity rises such that at 1 year of age it is roughly equal to the signal intensity of intervertebral disc. Above 1 year of age, the T1 signal intensity of red marrow should not be lower than that of intervertebral disc, and by 5 years of age red marrow signal intensity should exceed that of intervertebral disc (Sebag et al, 1993).

On proton density and T2-weighted images, the signal intensity of red marrow increases (probably as a result of its water fraction) and approaches that of yellow marrow on both conventional and fast spin pulse sequences. With short T1 inversion recovery (STIR) imaging or heavy T2-weighting (repetition time [TR] exceeding 3,000 ms and echo time [TE] > 90 ms), red marrow signal intensity may even exceed that of yellow marrow. Similarly, adding fat-saturation techniques to either conventional or fast spin pulse sequences causes red marrow to appear higher in signal intensity than yellow marrow on proton density and T2-weighted images (even with TR as low as 1,500 ms and TE as low as 60 ms) (Volger III and Murphy, 2006).

Muscle and red marrow will appear approximately equal in signal intensity with fat saturation on proton density images; however, red marrow will typically appear higher in signal intensity on T2-weighted images with fat saturation. Thus, on T1-weighted pulse sequences in
normal individuals 5 years of age or older, yellow marrow will be higher in signal intensity than red marrow, which in turn is higher in signal intensity than muscle or nondegenerated intervertebral discs. With increasing repetition times and echo delays, the signal intensity of red marrow approaches that of yellow marrow, and both remain higher in signal than muscle but lower in signal than fluid (Volger III and Murphy, 2006).

On T2-weighted spin-echo and fast spin-echo images, red marrow generally demonstrates intermediate signal intensity lower than that of yellow marrow (Levine et al, 1994). The contrast between red and yellow marrow becomes less apparent than on T1-weighted spin-echo images. On fast spin-echo T2-weighted sequences, the signal intensity of fat remains elevated and confusion between focal fat areas and lesions in red marrow. Nullation of the fat signal may be necessary to restore unequivocal distinction of fatty areas. On fat-suppressed fast spin-echo T2-weighted and STIR images, red marrow shows signal intensity higher than that of yellow marrow (Figures 11, 12 & 13) (Vande Berg et al, 1998a).

Signal characteristics of red marrow are highly variable on gradient-echo images. With gradient echo sequences, images can be obtained by choosing an echo time at which the phases of water and fat are either opposed (opposed-phase images) or parallel (in-phase images) due to their difference in resonance frequency (chemical shift). Since red marrow contains approximately equivalent amounts of water and fat, the net difference in water and fat magnetization which controls the voxel signal approaches zero on gradient-echo images obtained at a moment when fat and water proton magnetizations are in opposite directions (opposed phase images) (intravoxel chemical shift effect) (Vande Berg et al, 1998a).
Having a more extensive blood supply, hematopoietic marrow enhances to a greater degree than fatty marrow after intravenous administration of gadolinium-containing agents, thus reducing the normal contrast between red and yellow marrow on enhanced T1-weighted images (without fat suppression). As a result, the signal intensity changes that occur with normal marrow conversion also become less apparent (Dwek et al, 1997). This differential enhancement is more evident in younger individuals and decreases with age as the cellularity of red marrow declines (Baur et al, 1997).

In adults, visual detection of marrow enhancement on T1-weighted images (without fat saturation) is not possible despite measurable signal intensity changes between unenhanced and enhanced images (Saifuddin et al, 1994). Adding fat suppression to gadolinium-enhanced T1-weighted pulse sequences results in the differential enhancement of red and yellow marrow, becoming more conspicuous at any age (Volger III and Murphy, 2006).

The boundaries between red and yellow marrow change rapidly in the first two decades of life and then more slowly thereafter, but continual change is the general rule. Varying fractions of cellular and fatty marrow can produce a spectrum of signal alterations on MR images. These changes at times result in an inhomogeneous appearance of the marrow, raising concern for the presence of disease. Several features of normal marrow may be helpful in its identification on T1-weighted images (Vande Berg et al, 1998a).
Review of literature

Figure (11) (a) Coronal T1-weighted spin-echo MR image of the pelvis of a 10-year-old boy showing that pelvic bones and femoral metaphyses have an intermediate signal intensity, higher than that of muscles and lower than that of femoral heads that contain fatty marrow. The signal intensity contrast between epiphyseal fatty marrow and metaphyseal red marrow is elevated. (b) On the corresponding T2-weighted spin-echo image, the signal intensity contrast between yellow and red marrow is much decreased, and the signal of red marrow remains lower than that of yellow marrow (Vande Berg et al, 1998).

Figure (12): (a) Coronal T1-weighted spin-echo MR image of the proximal humerus of a 39-year-old female showing intermediate signal intensity areas in the humerus metaphysis and in the subchondral area of the humeral head (arrows). (b) Coronal fast spin-echo T2-weighted image shows no signal intensity difference between red and yellow marrow. (c) On a coronal fat-saturated fast spin-echo T2-weighted MR image, red marrow has a high signal intensity, higher than that of fatty marrow (Vande Berg et al, 1998).
Figure (13): (a) Coronal T1-weighted spin-echo image of the right hip of a 37-year-old man shows an intermediate signal intensity area (arrow) in the femoral neck which probably corresponds to normal red marrow. (b) On the corresponding in-phase gradient-echo image, yellow and red marrow have the same signal. (c) On an out-of-phase gradient-echo image, the signal contrast between yellow and red marrow is elevated. On this image, signals from fat and water protons are opposed, and tissues with equivalent amounts of water and fat (like red marrow) have a low signal intensity (Vande Berg et al, 1998).
Localized areas of high or low signal intensity within the bone marrow probably reflect regions of focal fatty conversion or islands of increased marrow cellularity, respectively (Caldemeyer et al, 1996).

Areas of focal fatty conversion generally have a characteristic appearance and do not present diagnostic dilemmas. Islands of red marrow can be more problematic. These tend to be geographic or elongated in shape but generally not round. They have indistinct margins in younger patients (when marrow conversion is less advanced) and distinct margins in older patients (when marrow conversion is more advanced). The red marrow islands predominate in endosteal locations and tend to be symmetric within individual bones (and in the skeleton as a whole) (Schweitzer et al, 1993).

Histologic studies have demonstrated that conversion to fatty marrow first occurs centrally within a region of red marrow, leaving a focus of fat surrounded by a rim of cellular marrow. The MR equivalent of this histologic process is a central focus of high signal intensity (fat) within an island of low signal intensity (red marrow). This finding has been termed a bull's-eye sign. Although often subtle, when present, this sign becomes a useful indicator of normal marrow (Schweitzer et al, 1993).

Finally, areas of low signal intensity in the marrow space that are presumed to represent normal red marrow should show appropriate signal changes on T2-weighted images and after gadolinium enhancement. When the area of signal alteration in question falls within these parameters, it can be presumed to represent normal marrow, realizing that infrequently some pathologic conditions (i.e., myeloma) can be present when the marrow has a normal MR appearance. Thus, at times, confirmation of MR findings may be necessary with either bone marrow
biopsy or follow-up examinations when the clinical situation warrants (Volger III and Murphy, 2006).

MR Characteristics of red marrow heterogeneities observed in normal subjects (Figures 14 & 15) are:

1. Central spot of high signal intensity on T1-weighted images
2. Symmetric distribution of low signal intensity areas, parallel to the subcortical or subchondral bone
3. Elongated shape of the low signal intensity areas
4. Heterogeneity generally located in areas of relatively cellular red marrow.
5. Low signal on T2-weighted spin-echo and out-of-phase gradient echo images, intermediate signal intensity on fat suppressed images,
6. No or very discrete enhancement after injection of gadolinium.
7. No corresponding changes on CT images and bone scans
8. No change over time

Although none of these features can confidently exclude marrow infiltration, but most of them are observed in healthy patients (Vande Berg et al, 1998a).
Figure (14): Sagittal T1-weighted spin-echo images of (a) L3- and (b) L4 vertebral bodies of a 44-year-old-female showing discrete heterogeneities in red marrow appearance. The confluent red marrow areas are distributed in the same areas in the two vertebral bodies (large arrows). Within confluent areas of red marrow, islands of more fatty marrow are present (bull's-eye sign) (small arrow) (Vande Berg et al, 1998).

Figure (15): (a) Macroscopic section of two lumbar vertebral bodies obtained at autopsy from a 69-year-old male. Red areas correspond to hematopoietic tissue; yellow areas mainly located in the center of the vertebral bodies correspond to fatty marrow. (b) Sagittal T1-weighted spin-echo MR image of the specimen maps the distribution of red and yellow marrow. Areas of intermediate signal intensity in the vertebral bodies correspond to the red marrow areas on the section; areas of high signal intensity correspond to fatty marrow (Vande Berg et al, 1998).
MR CONVERSION PATTERNS OF BONE MARROW IN DIFFERENT ANATOMICAL REGIONS

Bone marrow can be regarded as a balanced system in which fat and nonfat cells cohabitate and in which yellow and red marrow can be enlarged or diminished as part of a physiologic phenomenon. Normal bone marrow is dynamic, and this produces a wide spectrum of appearance of bones in MRI. Understanding of these changes is a prerequisite to the interpretation of MR images of bone marrow pathology (Vande Berg et al, 1998a).

An important consideration in interpreting MR marrow data is the well-established phenomenon of the normal, progressive conversion of red to yellow marrow with aging (Ricci et al, 1990). Understanding of the MR characteristics of fatty and hematopoietic marrow, in conjunction with knowledge of the type of marrow that is normally present in a given bone at a given age, will allow recognition of any local or diffuse marrow abnormality (Lawson et al, 1994).

Skull:

Three patterns of marrow distribution were identified. Pattern (1) is characterized by bone marrow of uniformly low signal intensity or, at most, the presence of very small areas of high signal intensity in frontal and occipital bones. In pattern (2), frontal and occipital bones have uniformly high signal intensity, and patchy areas of high intensity appear in the parietal bone. In pattern (3), the entire skull has uniformly high intensity. Pattern (1) is found predominantly in the youngest age group (younger than 10 years). Patterns (2) and (3) have a relatively uniform distribution with age (Figure 16) (Ricci et al, 1990).

In the skull, MR conversion of red to yellow marrow occurs early, generally before 20 years of age, and appears to be more prominent in the frontal and occipital bones. MR evidence of red marrow in the parietal
bones persists later in life in some individuals. Many patients, however, will demonstrate only fatty marrow in the entire diploic space on MRI as early as the second decade of life (Volger III and Murphy, 2006).

In the facial bones, the maxilla and zygoma contain fatty marrow only, whereas the ethmoid bone does not have any marrow tissues at all. The mandible, on the other hand, still contains hematopoietic marrow in adults (Kricun, 1985).

In the mandible: At birth, hematopoietic marrow is distributed throughout the mandible. Conversion has occurred by age 3 years in the most distal part of the mandible and the mental region, followed by the body, the angle, and the ramus of the mandible. The condyle, the most proximal part of the mandible, contains hematopoietic marrow at age 25. These results suggest that conversion in the mandible closely corresponds to changes occurring in the long tubular bones, in which conversion occurs first in the proximal and distal epiphyses, followed by the diaphysis, distal metaphysis, and proximal metaphysis (Figure 17) (Yamada et al, 1995).
**Figure (16):** T1-Weighted MR images of skull bone marrow distribution patterns. (a) Pattern 1. Hematopoietic marrow of all low signal intensity or small areas of fatty marrow of high signal intensity are seen in frontal and occipital regions in an 11-year-old girl. (b) Pattern 2. Fatty marrow is seen in the frontal and occipital regions, and mixed signal intensity is seen in the parietal region in a 42-year-old woman. (c) Pattern 3. Essentially all high-signal-intensity fatty marrow is seen in a 70-year-old man. *(Ricci et al, 1990).*

**Figure (17):** Marrow map of mandible from birth to adulthood shows sequence of marrow conversion with age. Distributions of hematopoietic (red) marrow and fatty (yellow) marrow are represented by visual grading based on merged criteria of signal intensity (SI) and homogeneity on T1-weighted MR images. *(Yamada et al, 1995).*
Spine:

Marrow signal intensity in vertebral bodies (sites where the red marrow fraction remains relatively high throughout life) is lower than marrow signal intensity in the distal appendicular skeleton where little red marrow persists in adulthood. In the normal individual, the red/yellow marrow and trabecular bone fractions turn over continuously but change slowly throughout life. This is reflected by the changing marrow appearance seen on MR images in patients of various ages. The general pattern of change observed on T1-weighted images is one that begins with vertebral marrow displaying diffuse low signal intensity (lower than intervertebral discs) in patients up to 1 year of age (Sebag et al, 1993).

From 1 to 5 years of age, the marrow is roughly equal in signal intensity with intervertebral disc. Conversion of red marrow then proceeds focally and diffusely within the vertebral body. Described focal patterns include basivertebral and band patterns. In the former, a triangular area of fat conversion appears around the exit site of the basivertebral vein, whereas the latter (possibly a variation of the basivertebral pattern) displays a band of high signal fat conversion centrally in the vertebral body. These patterns are generally observed in children (older than 5 years) and young adults (Volger III and Murphy, 2006).

Ricci et al, (1990) described four main patterns of marrow distribution throughout the spine. In pattern 1, the vertebral body has uniformly low intensity except for linear areas of high intensity superior and inferior to the basivertebral vein. In pattern 2, band like and triangular areas of high signal intensity are found in the periphery, that is, near the end plates anteriorly and posteriorly at the corners of the vertebral bodies. In pattern 3, there are diffusely distributed areas of high intensity, consisting of either numerous indistinct dots measuring a few
millimeters or less (pattern 3a), or fairly well marginated areas ranging in size from 0.5 to 1.5 cm (pattern 3b). In a few cases, marrow distribution in the spine could best be described as a combination of patterns 2 and 3a or 3b (Figure 18).

Ricci et al, (1990) categorized these patterns in the cervical, thoracic, and lumbar spine as following: In the cervical spine, the majority of patients with pattern 1 were younger than 40 years. The majority of patients with pattern 2 or 3 were older than 40 years. In the thoracic spine, the majority of patients with pattern 1 were younger than 30 years, and of those with pattern 2 were older than 50 years. In the thoracic spine, the age distribution of patients with pattern 3 was relatively uniform. A pure pattern 2 was not seen in the thoracic spine. In the lumbar spine, pattern 1 was again found primarily in younger age groups. The frequencies of patterns 2 and 3 show a monotonic increase with age (most of pattern 2 and pattern 3 was found in patients older than 40 years).

Fatty marrow can appear near the end plates presumably due to mechanical stress or degenerative disc disease. This pattern is seen more commonly in the cervical and lumbar regions. Variable sized foci of fatty marrow can also occur diffusely distributed throughout the vertebral body. These patterns occur with greater frequency in patients older than 40 years and both may be present at the same time (Volger III and Murphy, 2006).

Diffuse conversion in the vertebral body is evidenced by a gradual increase in T1 signal intensity. For example, measured T1 relaxation times of vertebral bodies decline with age (Dooms et al, 1985), probably reflecting a decreasing fractional volume of hematopoietic marrow with concomitant increase in fatty marrow. This shortening of T1 values is most pronounced in the first four decades of life when normal conversion
of red to yellow marrow occurs. Beyond the fourth decade, loss of trabecular bone mass and the resultant reduction of vertebral mineral content (by approximately 40% in men and 55% in women by age 75) contributes to the decline in T1 values. T2 relaxation times show a similar decline with age. Differential loss of trabecular bone with replacement by fat cells as occurs in osteoporosis may help explain differences in the range of T1 and T2 values for men and women that is similar under the age of 40 years but slightly higher in women after 50 years of age (Volger III and Murphy, 2006).
Figure (18): Short TR/TE MR images and schematics of spinal bone marrow distribution patterns. (a) **Pattern 1.** High-signal-intensity fatty marrow is seen confined to linear areas along the basivertebral vein in a 14-year-old girl. (b) **Pattern 2.** Band like and triangular areas of fatty marrow are located peripherally in a 59-year-old man. (c) **Pattern 3a.** Multiple small areas of high-signal-intensity fatty marrow are seen in a 60-year-old woman. (d) **Pattern 3b.** Multiple, relatively large, fairly well marginated areas of fatty marrow are seen in a 42-year-old woman. *(Ricci et al, 1990).*
Pelvis (Figure 19):

Age-related marrow changes in the pelvis manifest as early conversion of red to yellow marrow in the acetabular regions and anterior ilium and more gradual conversion throughout the remainder of the pelvis (Dawson et al, 1992). Fatty marrow appears in the anterior ilium and acetabular areas before 5 years of age, resulting in a heterogeneous MR pattern of the marrow at these sites. This conversion of red to yellow marrow occurs with such reliability that the absence of such a finding by 5 years of age should prompt further investigation. Marrow signal intensity and heterogeneity on T1-weighted images in the remainder of the pelvis increase with age and correlate with increased fractions of microscopic fat in the marrow. Areas of confluent red marrow evolve to increasingly well-defined islands in older patients (Levine et al, 1994).

At or around the sixth decade, residual hematopoietic marrow is found predominately in the posterior iliac crests and sacrum (sacral vertebral bodies and sacral ala adjacent to the sacroiliac joints) with very little identifiable cellular marrow remaining in the acetabular regions and symphysis pubis. The reverse pattern (higher fractions of red marrow being observed in symphyseal and acetabular areas than in the sacrum and posterior iliac regions) is uncommon in normal individuals and should raise concern for pathologic marrow processes (Levine et al, 1994). Gender-related differences of red and yellow marrow in the sacrum have been described and generally identify the red marrow fraction as being larger and more cellular in women (Duda et al, 1995).

Appendicular Skeleton:

At sites where red marrow is present, a variety of signal patterns may be observed, reflecting relative red/yellow marrow fractions and distribution. A common pattern observed is islands of red marrow scattered throughout a background of fatty marrow. The islands may have
a variety of configurations ranging from small and elongated to large and geographic. Less commonly in the long bones, foci of yellow marrow are evident in a background of red marrow, resembling the phenomena of focal fat conversion in the vertebral bodies (Volger III and Murphy, 2006).

In the appendicular skeleton and in individual long bones, common local MR marrow patterns also exist. The humerus and femur warrant special attention. They are the long bones that consistently contain the greatest residual concentration of hematopoietic marrow in adults and are the sites of transition between the "fatty" appendicular marrow and the "hematopoietic" axial marrow. In these bones, red marrow is commonly found in the proximal two thirds with the greatest fraction usually in the proximal one third. Less commonly, foci of red marrow may be evident in the distal one third of these bones. This finding, by itself, should not be considered abnormal (Volger III and Murphy, 2006).

MR patterns reflecting the balance of red and yellow marrow fractions in the shoulder change throughout life. Normal red to yellow marrow conversion occurs early in the distal epiphysis, distal metaphysis, and diaphysis and is often complete by age 6 years (Zawin and Jaramillo, 1993). Red marrow persists in the proximal humeral metaphysis in most patients until late in life (at least the seventh decade). In a smaller number of normal individuals, it can be found in the proximal humeral epiphysis. This occurs more frequently in younger patients. Similarly, although red to yellow marrow conversion begins early in the acromion (an epiphyseal equivalent) and continues throughout life, residual red marrow may also be found at this site. In the glenoid, conversion begins later, progresses more slowly, and remains incomplete throughout life (Volger III and Murphy, 2006).
**Femur:**

*Ricci et al; 1990* stated that there are four patterns recognized in the proximal femur. **Pattern (1a)** is characterized by uniformly high intensity only in the epiphysis and the greater and lesser trochanters. In **pattern (1b)**, high signal intensity is seen also in a triangular area inferior to the femoral head medially, and fatty marrow extends into a portion of the intertrochantenic region just medial to the greater trochanter. In **pattern (2)**, areas of high intensity are seen in the intertrochantenic region, consisting of many small hyperintense foci that are partly confluent in some cases. In **pattern (3)**, signal intensity is uniformly high throughout the proximal femur. In patterns 2 and 3, the triangle of Ward was often seen bounded by three rays of prominent trabeculae. The frequency of pattern 1 progressively decreases with age. Pattern 2 has a maximum frequency in the middle age group (most of cases are younger than 50 years) and progressively rises and falls before and after the peak, respectively. The frequency of pattern 3 increases with age (most of cases are older than 50 years) *(Figure 20)*.

In the femora, increased signal intensity (fatty marrow) is apparent in the diaphyseal marrow by age 5 years or younger, whereas unequivocal fatty marrow is present in the diaphysis before age 10 years *(Moore and Dawson, 1990)*. The absence of diaphyseal fatty marrow at age 10 years or older is distinctly unusual and requires further investigation to exclude underlying marrow disease. In the distal femoral metaphysis, a homogeneous red marrow MR pattern after 25 years of age is atypical and requires explanation if encountered. However, geographic or spotty areas of red marrow can be observed in the distal femoral metaphyses of men and women at almost any age. This finding can be encountered in approximately one half of female and one sixth of male patients. Metaphyseal red marrow has a higher prevalence in women between the
ages of 40 and 60 years, whereas no age prevalence appears to exist in men. Other settings in which persistent or reconverted foci of red marrow have been recognized in the distal femoral metaphysis include young patients (under 39 years of age), marathon runners, heavy smokers (more than one pack per day), and obese women (>78 kg) who smoke (Wilson et al; 1996).
Figure (19): Schematics of age-related marrow patterns in the pelvis. (a) Fatty marrow is observed in the acetabular regions early in life, usually before 5 years of age. (b) With age, fatty marrow appears in larger fractions at other locations throughout the pelvis, particularly adjacent to the sacroiliac joint (Ricci et al., 1990).

Figure (20): Short TR/TE MR images and schematics of proximal femur marrow distribution patterns. (a) Pattern 1a. High-signal-intensity fatty marrow confined to the capital femoral epiphysis and greater and lesser trochanters in a 15-year-old boy. (b) Pattern 1b. In addition to the areas seen in pattern 1a, fatty marrow is seen in a triangular region inferior to the medial portion of the femoral head and in the lateral portion of the intertrochanteric region adjacent to the greater trochanter in a 27-year-old woman. (c) Pattern 2. Many small, confluent, regions of high-signal-intensity fatty marrow are seen in the intertrochanteric region in addition to the fatty regions of pattern 1 in a 45-year-old woman. (d) Pattern 3. Uniform, high-signal-intensity fatty marrow occupies essentially the entire proximal femur in a 60-year-old man. Quoted from Ricci et al., 1990.
PATHOLOGY OF BONE MARROW INFILTERATIVE LESIONS

Classification of Diffuse Marrow Disorders:

Bone marrow responds to insult and disease through a select number of mechanisms. These pathophysiologic responses can be identified and categorized on MR images. The concept provides a useful means of grouping the various disorders that affect marrow and for understanding associated marrow signal patterns. Five pathophysiologic mechanisms are considered:

1- Reconversion: where yellow marrow is "reconverted" to red marrow, Red marrow hyperplasia is a subcategory of this mechanism.
2- Myeloid depletion: all marrow cells other than fat are destroyed or disappear.
3- Ischemia, all marrow elements die and are repaired to a greater or lesser degree.
4- Infiltration: when pathologic cells invade normal marrow.
5- Marrow edema: in where excess water appears in the marrow tissue (Volger III and Murphy, 2006).

An alternative classification system has been proposed by Vande Berg et al; 1998b. In this system, T1-weighted images are used to classify marrow disorders into four patterns: marrow depletion, infiltration, replacement, and signal void. These four patterns can be observed alone or together in a focal, regional, or diffuse skeletal distribution. Marrow disorders are then grouped according to their typical MR signal characteristics and distribution.

Metastases:

Bone metastases are the most common malignant bone tumor. Skeletal involvement occurs in 30%–70% of all cancer patients,
with breast cancer being the leading cause for bone metastases in women and prostate cancer in men, followed by lung cancer \textit{(Padhani and Husband, 1998)}. Bone metastases may occur with almost all malignancies, but they are most common in carcinomas of the breast (47–85%), lung (32%), prostate (54–85%), kidney (33–40%), or thyroid (28–60%) \textit{(Galasko, 1986 and Marcove and Arlen, 1992)}.

In adults, marrow metastases most commonly result from carcinoma of the prostate, breast, lung, kidney, gastrointestinal tract, and melanoma of the skin. In pediatric patients, the most common primaries that metastasize to the marrow are neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma. Marrow invasion occurs by hematogenous dissemination, and the high frequency of metastases to the pelvic bones, vertebrae, and sternum is attributed to the abundant vascular supply afforded by the vertebral venous plexus, which serves as a major venous pathway. Metastatic tumor deposits in the marrow can be accompanied by necrosis, fibrosis, bone destruction (osteolytic activity), or bone production (osteoblastic activity) \textit{(Bredella and Stoller, 2007)}.

The spine is the most common site of skeletal metastases (39%) because of the abundant vascularization and red bone marrow. Most bone metastases are hematogenous in origin. The initial seeding of metastatic deposits via hematogenous spread is typically localized in the hematopoietic (red) marrow. This location explains the predominance of metastatic bone lesions in the axial skeleton (>90% of metastatic bone lesions) \textit{(Taoka et al, 2001)}.

Detection of tumor bone metastases is essential for optimal therapy. The purpose of imaging is to identify bone metastases as early as possible, to determine the full extent of disease, to evaluate the presence of complications that may accompany malignant bone involvement (including pathologic fractures and spinal cord compression), to monitor
response to therapy, and, occasionally, to guide biopsy if histologic confirmation is indicated (Even-Sapir, 2005).

Bone involvement by cancer occurs most commonly by hematogenous spread. The venous system is the main pathway for transport of tumor cells to the skeleton, although tumor may occasionally extend directly from the soft tissue to the adjacent bone (Morgan-Parkes, 1995).

The vast majority of bone metastases initiate as intramedullary lesions. Over 90% of bone metastases are found in the distribution of the red active marrow, which is located in the axial skeleton, in adults. The normal bone undergoes constant remodeling, maintaining a balance between osteoclastic (resorptive) and osteoblastic activity. As the metastatic lesion enlarges within the marrow, the surrounding bone undergoes osteoclastic and osteoblastic reactive changes. Based on the balance between the osteoclastic and osteoblastic processes, the radiographic appearance of a bone metastasis may be lytic, sclerotic (blastic), or mixed. The osteoblastic component of the metastasis represents reaction of normal bone to the metastatic process. Rapidly growing aggressive metastases tend to be lytic, whereas sclerosis is considered to indicate a slower tumor growth rate. Sclerosis may also be a sign of repair after treatment (Even-Sapir, 2005).

**Plasma cell dyscrasias:**

Plasma cell dyscrasias are a heterogeneous group of clinical disorders characterized by the production of a specific immunoglobulin molecule that is unique for each patient. The role of MR imaging has been evaluated in each one of these disorders (Moulopoulos and Dimopoulos, 1997).

Plasma cell neoplasms are a group of diseases in which proliferation and accumulation of immunoglobulin-secreting cells occur in the bone
Review of literature

marrow and in which a monoclonal protein is generally detected in the blood and/or in urine (Vande Berg et al., 1998c). Ambrosino et al., 1992 mentioned that multiple myeloma is the most common of the plasma cell dyscrasias. It is also the most common primary bone tumor in adults (Brown, 1993, Amour et al., 1994 and Bredella and Stoller, 2007).

**Multiple myeloma:**

Multiple myeloma is a malignant disorder of plasma cells that affects the bone marrow. It is usually associated with the presence of a monoclonal immunoglobulin in the serum and/or urine and with the presence of lytic bone lesions (Moulopoulos et al., 2005).

Myeloma is the most common primary bone malignancy. It accounts for 10% of all hematological malignancies and 1% of all cancers. In the United States, there are an estimated 16,000 new cases and over 11,000 deaths yearly due to myeloma (Mulligan and Badros, 2007). The median age at diagnosis is 65 years, and about 3% of patients are younger than 40 years. The disease has a higher incidence in men and African Americans. (Angtuaco et al; 2004).

The hallmark of MM is the detection in blood and/or urine of a monoclonal protein, M protein, produced by the abnormal plasma cells. Serum protein electrophoresis reveals a localized band in the globulin part of the \(\alpha\)(immunoglobulin [Ig] A) or \(\gamma\)(IgG) region in 80% of patients. The remaining 20% of patients will have either hypogammaglobulinemia or a normal-appearing pattern (nonsecretory type). By using the more sensitive techniques of immunofixation and immunoelectrophoresis, M protein (in serum or/and urine) will be detected in 99% of patients. The IgG isotype is seen in 60% of MM patients; the IgA isotype, in 25%; the IgD isotype, in 1%; the IgM isotype in 1%; and light chain disease, in 20% (Edgardo et al., 2004).

Plasma cell dyscrasias manifest themselves in a variety of forms
that range from MGUS (monoclonal gammopathy of undetermined significance) and smoldering myeloma that require no therapy, to the “malignant” form of multiple myeloma. The role of imaging in the management of myeloma includes: an assessment of the extent of intramedullary bone disease, detection of any extramedullary foci, and severity of the disease at presentation; the identification and characterization of complications; subsequent assessment of disease status. (Mulligan and Badros, 2007).

Multiple myeloma initially arises in red haematopoietic marrow, which in the spine is abundant in the vertebral bodies. The pedicles are not involved initially due to paucity of red marrow in this location. In later stages of multiple myeloma there is conversion of yellow to red marrow, and lesions may be found in the pedicles, in the posterior element, and even in the distal extremities (Kricun, 1985).

**Plasmacytoma:**

Solitary myeloma is plasma cell tumor that manifest as a single mass of marrow involvement. Solitary myeloma is diagnosed in patients at a mean age of about 50 years, in contrast to multiple myeloma, in which the age range is 50–70 years. Solitary myeloma may progress over time to multiple myeloma (Tateishi et al; 2003).

Less than 5% of patients with a plasma cell dyscrasia present with a single bone plasmacytoma (SBP) or extramedullary plasmacytoma (EMP) due to a malignant plasma cell infiltrate, without apparent evidence of systemic myeloma. Most present with a painful lesion, but some patients who are asymptomatic may be diagnosed during radiologic examination for other conditions (Weber, 2005).

Solitary plasmacytoma is an uncommon tumor occurring in 3-7%
of patients with plasma cell neoplasms. The lesion is commonly found in the axial skeleton and is predominantly lytic in appearance (Major et al; 2000). Yochum and Rowe, 1996 stated that the mandible, ilium, vertebrae, proximal femur and scapula are the favored sites of involvement in plasmacytoma.

The diagnosis of SBP requires a solitary bone lesion, a biopsy of which shows infiltration by plasma cells; negative results on a skeletal survey; absence of clonal plasma cells in a random sample of bone marrow; and no evidence of anemia, hypercalcemia, or renal involvement suggesting systemic myeloma (Dimopoulos et al; 2000).

**Lymphoma:**

Lymphomas represent neoplastic proliferation of the lymphoid cells that normally reside in primary lymphoid tissue such as lymph nodes. The two major types of lymphomas are Hodgkin disease and non-Hodgkin lymphoma. Bone marrow examination is an important component of the staging process for patients with malignant lymphoma (Bredella and Stoller, 2007).

Lymphomas represent about 4% of the new cases of cancer diagnosed in the United States every year, making them the fifth most common type of cancer and the fifth leading cause of cancer death. Lymphoma can affect any region of the body. Most patients present with lymphadenopathy, focal or diffuse organ involvement, or generalized multiorgan involvement (Rademaker, 2007). In Egypt, the frequency of malignant Lymphoma varies between 7.8% to 12% of cancer cases according to the registries of various cancer centers (Ibrahim and aref, 1984 and Mokhtar, 1991). In the NCI-Egypt cancer pathology registry, the ratio of NHL to HL was 2.3: 1 and HL constituted 30.3% of all lymphoma cases (Mokhtar and Khaled, 2002). A similar figure of about 30% was reported in other Egyptian series (Tawfik and Aboul Elsa, 1982).
Hodgkin’s disease (HD) has a bimodal incidence curve and occurs more frequently in two separate age groups, the first being young adulthood, the second being in those over 50 years old. About one third of people with HD have systemic symptoms, such as low-grade fever, night sweats, weight loss, pruritus, or fatigue (Rademaker, 2007).

Infiltration of the bone marrow occurs in 5% to 15% of patients with Hodgkin's disease and in 25% to 40% of patients with non-Hodgkin's lymphoma. The diagnosis of bone marrow involvement is established with bone marrow biopsies, which are usually obtained from the posterior superior iliac crest. Sampling errors exist even with bilateral iliac crest biopsies, because only a small volume of the bone marrow is examined (Moulopoulos and Dimopoulos, 1997).

**Hodgkin Disease:**

Hodgkin disease is distinguished by the following characteristics: Localization to a single group of lymph nodes (i.e., cervical, cervicoclavicular, mediastinal, or para-aortic), Bimodal age distribution, Infrequent extranodal (e.g., bone marrow, CNS, gastrointestinal tract, or skin) involvement, Focal rather than generalized presentation in the marrow, An associated soft-tissue component is common, Spinal disease often presents with sclerosis of a vertebral body (“ivory vertebral body”) (Bredella and Stoller, 2007).

The unifying histopathologic feature of Hodgkin disease is the presence of Reed-Sternberg cells, which are large cells with a bilobed nucleus exhibiting prominent nucleoli set in a polycellular background of inflammatory cells and often fibrosis. Although four distinct histologic subtypes of Hodgkin disease have been identified (lymphocyte predominant, nodular sclerosis, mixed cellularity, and lymphocyte depleted), the prognosis rests primarily in the clinical and pathologic
stage of disease rather than its histologic subtype \textit{(Bredella and Stoller, 2007)}.

\textbf{Non-Hodgkin Lymphoma:}

Malignant lymphomas other than Hodgkin disease are referred to as non-Hodgkin lymphoma. Within this classification is a diverse group of diseases that span various morphologic and immunologic types. They range from low-grade indolent processes to highly aggressive lesions that, if left untreated, are rapidly fatal. The various types of non-Hodgkin lymphoma differ in their response to therapy. In contrast to Hodgkin disease, the prognosis of non-Hodgkin lymphoma is more directly related to the histologic subtype than to the clinical and pathologic stage \textit{(Bredella and Stoller, 2007)}.

Low-grade non-Hodgkin lymphoma, notably small cleaved cell lymphoma and well-differentiated small lymphocytic cell lymphoma, has a high incidence of marrow involvement. When initially diagnosed, low-grade non-Hodgkin lymphoma almost always involves widespread lymph nodes at multiple sites in an asymmetric distribution above and below the diaphragm. In 50\% of cases, the bone marrow is affected at the time of diagnosis. On a microscopic level, small cleaved cell lymphomas tend to be focal and patchy and form nodules in a peritrabecular location. Splenic involvement is usually in the form of small miliary nodules centered in the white pulp zones. Marrow involvement in well-differentiated small lymphocytic lymphoma is most commonly diffuse or interstitial \textit{(Bredella and Stoller, 2007)}.

High-grade non-Hodgkin lymphoma (including large cell lymphoma) may be designated as histiocytic or reticulum cell (large cell), immunoblastic, lymphoblastic, Burkitt, or non-Burkitt lymphoma. Morphologically and immunologically, high-grade non-Hodgkin lymphoma is the most heterogeneous type of lymphoma. It is the most
common primary lymphoma arising in bone and is the type that occurs most often in acquired immunodeficiency syndrome (AIDS). In contrast to the low-grade (i.e., small cleaved cell) lymphoma, microscopic marrow involvement in high-grade lymphoma can be focal or widespread, but there is no peritrabecular bony preference (*Bredella and Stoller, 2007*).

A rapidly growing mass at a single nodal or extranodal site is the typical clinical presentation in large cell lymphoma. Liver and spleen involvement, not common at the time of diagnosis, consists of large masses, as opposed to the small miliary nodules typical of low-grade lymphomas. Large cell lymphomas are rapidly fatal if not treated. However, with aggressive multiagent chemotherapy, complete remission can be achieved in 60% to 80% of patients. In contrast, low-grade lymphoma is relatively resistant to chemotherapy, although it exhibits an indolent clinical course (*Bredella and Stoller, 2007*).

Non-Hodgkin’s lymphoma (NHL) is a heterogeneous group of diseases of either B-cell or T-cell origin. NHL represents the second fastest growing cancer in the United States, and the most commonly occurring hematologic cancer. The incidence of NHL in the United States has increased by 50% over the past 15 years, and the cause for this increase is not known. Overall, NHL has a worse prognosis than HD. Unlike HD, which commonly spreads through contiguous groups of lymph nodes, NHL is infrequently localized at the time of diagnosis and frequently involves extranodal sites of disease (*Rademaker, 2007*).

**Primary lymphoma of bone:**

Primary lymphoma of bone is characterized by lymphomatous involvement of the medullary cavity of a single bone, without concurrent lymph node or visceral involvement, for at least 6 months. It is important to differentiate primary lymphoma of bone from skeletal involvement in systemic lymphoma, since it has a better prognosis and is treated
differently than systemic lymphoma (Bredella and Stoller, 2007).

Primary lymphoma of bone constitutes approximately 5% of all extranodal non-Hodgkin's lymphomas and 5-7% of primary bone tumors. Initially, the term "reticulum cell sarcoma" is used for this type of neoplasm. According to the currently used classification, almost all primary lymphomas of bone are B cell non-Hodgkin's lymphoma with a diffuse mixed cell or diffuse large cell histology. Primary lymphoma of bone responds well to combined chemotherapy and adjuvant local radiation therapy or, alternatively, to chemotherapy alone. The reported 5-year survival rate after combined therapy is better than 90% (Mengiardi et al; 2005).

Although osseous involvement of disseminated malignant lymphoma is not uncommon, primary lymphoma of bone is infrequent. The diagnosis implies the exclusion of any evidence of nodal or disseminated disease on the basis of modern staging techniques. Primary bone lymphoma occurs in a broad range of patients, with a median range, 36–52 years, with peak prevalence among patients in the 6th to 7th decades of life. It is rare in patients younger than 10 years and occurs slightly more often in males (male-to-female ratio, 1.5 to 1). Male children also appear to be affected more frequently than female children (6:1 ratio). The femur is the most common site (especially the metadiaphysis) and is affected in 25% of cases. Other sites include the pelvis, humerus, head and neck, and tibia. Vertebral involvement is not unusual (Krishnan et al; 2003).

**Leukemia:**

Leukemia is characterized by neoplastic growth of hematopoietic cells. The bones with the greatest amount of blood-forming marrow are most often involved (Kaiser and Ramos, 1990). Leukemias are divided into acute and chronic. Acute leukemias represent an accumulation of
immature (blast) cells owing to a defect in the ability to produce mature cells. Chronic leukemias result from massive proliferation of mature cells (Resnick and Haghighi, 1995).

Leukemia is a disease of the bone marrow. It occurs at any age and represents one of the most common forms of malignancy in childhood. (Valvassori et al; 1999).

The leukemias have been classified into acute and chronic and further divided and subdivided into multiple diagnostic categories. The hallmark of acute leukemia is the presence of increased numbers of blasts in the peripheral blood or bone marrow. The number of blasts should exceed 30% in the peripheral blood or 30% of the total nucleated marrow elements in the bone marrow to establish a diagnosis of acute leukemia (Schumacher et al; 2002).

Acute leukemias are the 20th most common cause of cancer deaths at all ages and as a group represent the most common malignant disease in childhood. This aggressive group of disorders arises at the primitive stem cell level and is usually classified as either lymphocytic or myelogenous in type, based on the cytologic features of the blast cell. Further classification of the leukemic blasts, based on immunologic markers, cytogenetics, and electron microscopy, provides useful prognostic and therapeutic information. Eighty percent of patients with acute lymphocytic (lymphoblastic) leukemia are children, and 90% of patients with acute myelogenous leukemia are adults (Bredella and Stoller, 2007).

The majority of acute leukemias arise de novo, although they may represent the final stage of a progression from a preleukemic state (i.e., myelodysplasia) or the end stage of a chronic myeloproliferative disorder such as chronic myelogenous leukemia. The distinguishing feature of the acute phase is the uncontrolled growth of poorly differentiated blast cells.
These cells rapidly accumulate in the marrow, suppressing the normal marrow elements and resulting in the commonly observed clinical symptoms of fatigue, weakness, infections, and hemorrhage (Bredella and Stoller, 2007).

Clinical assessment of leukemia involves posterior iliac crest aspiration for bone marrow biopsy and peripheral blood smear analysis. Peripheral disturbances in hematopoiesis are often nonspecific and frequently occur prior to significant increases in marrow blast cells. In relapse, acute leukemia may present with focal or irregular areas of infiltration, which may represent surviving rests of treated tumor cells. This appearance is more patchy and irregularly margined than that usually seen with focal metastatic disease (Bredella and Stoller, 2007).

Acute lymphoblastic leukemia accounts for 80% of all cases in children and 30% in adults. About 80% arise from B-cell lineage and 20% from T cell. Acute myeloid leukemia (AML) is more common in adults, although it represents 20% of the cases in children. Chromosome abnormalities are detected in most cases. Chronic lymphatic leukemia (CLL) is a disease of adulthood, mostly of the B-cell lineage, usually characterized by an indolent course. Large granular lymphatic leukemia is the T-cell lineage counterpart, also showing a benign clinical course. Chronic myelogenous leukemia may occur in children and has a worse prognosis than CLL (Valvassori et al; 1999).

Acute leukaemia is the commonest malignancy of childhood. In adults, chronic leukaemias predominate but sometimes may terminate in an acute blastic form. Radiographic demonstration of bone lesions in children is relatively common and reflects both the widespread extent of red marrow and the active bone turnover in the growing skeleton. Skeletal lesions in adults tend to be uncommon and focal, often simulating carcinomatous metastases. Skeletal deposits from the relatively benign
lymphatic leukaemia of the elderly are rare (Stoker and Saifuddin, 2001).

The acute disease is often insidious, with nonspecific malaise, anorexia, and weight loss. Pain in the limbs is common and probably related to the radiological changes; however, pathological fractures are common. Bone pain at the time of presentation is five times more common in children than adults (Stoker and Saifuddin, 2001).

Although the diagnosis is usually made from the blood film, aleukaemic forms exist. Examination of sternal marrow is essential and may have to be repeated if initially negative (Stoker and Saifuddin, 2001).

Clinically, patients with leukemia present with fever, edema, enlarged lymph nodes, and joint pain unresponsive to salicylates. The diagnosis is made by examining the peripheral blood or bone marrow and finding an increased number of lymphoblasts (Miller and Hoffer; 2001).

Bone lesions accompanying leukemia affect all age groups but are most frequently seen in patients in the first decade of life. Whereas all bones can be affected with leukemic lesions, most likely sites include the femur, ilium, spine, humerus, tibia, scapula, and rarely the skull (Miller and Hoffer; 2001).
**Chronic Leukemias:**

In contrast to acute leukemias, the malignant cell line in chronic leukemias has a limited capacity for differentiation and function in the initial stages of the disease process. As the disease progresses, thrombocytopenia and granulocytopenia develop, as they do in patients with acute leukemia. Compared with acute leukemias, the chronic leukemias are characterized by a long course with prolonged survival. As mentioned, chemotherapy, which is used aggressively in acute myelogenous leukemia and produces significant bone marrow hypoplasia or aplasia, has a secondary role in the management of chronic leukemias, which tend to have a more indolent course (*Bredella and Stoller, 2007*).

**Chronic Lymphocytic Leukemia:**

Chronic lymphocytic leukemia represents the most common form of leukemia in the United States; it is twice as common as chronic myelogenous leukemia. Ninety percent of patients with chronic lymphocytic leukemia are more than 50 years of age, and the disease shows a male predilection. Lymph node involvement is present in the majority of patients. Chronic lymphocytic leukemia is characterized by abnormal clones of immunologically incompetent lymphocytes. Patients may be asymptomatic or the disease may be stable at the time of diagnosis; in this case, treatment with alkylating agents is withheld. Although bone marrow analysis is not required to establish the diagnosis, examination reveals a hypercellular marrow with morphologically mature lymphocytes (*Bredella and Stoller, 2007*).

**Hairy Cell Leukemia**

Hairy cell leukemia, representing 2% of all leukemias, is a form of chronic leukemia that evolves from B lymphocytes. It typically occurs in men and classically presents as pancytopenia with splenomegaly. The distribution of marrow involvement is irregular and patchy, with a
propensity for focal marrow involvement. Focal or extensive involvement with reticulin limits productive marrow aspirations. Bone core biopsy, the definitive diagnostic procedure, reveals mononuclear cells in clusters or sheets within a fine reticulin mesh in a patchy or diffuse pattern. The marrow may be hypercellular or hypocellular (Bredella and Stoller, 2007).

Hairy cells are reactive to tartrate-resistant acid phosphatase, which distinguishes hairy cell leukemia from other lymphoproliferative malignancies. MR imaging demonstrates both a patchy lymphoma-like marrow pattern and a second pattern with a diffuse marrow infiltrate that resembles the distribution of chronic myelogenous leukemia (Bredella and Stoller, 2007).

**Myeloproliferative Disorders:**

The myeloproliferative disorders, a form of chronic leukemia, are a group of syndromes characterized by abnormal proliferation of bone marrow cell lines, which all arise from a common pluripotential stem cell. These stem cells produce the progenitor erythroid, granulocytic, monocytic, and megakaryocytic cell lines. The myeloproliferative syndromes include polycythemia vera, primary myelofibrosis with myeloid metaplasia, essential thrombocythemia, and chronic myelogenous leukemia. All of these disorders result in new clones that have a proliferative advantage over the normal marrow cells, which they gradually replace, and all have genetic instability, which predisposes to the development of an acute leukemia. The probability of progression to acute leukemia is greatest in chronic myelogenous leukemia, leading to chronic myelogenous leukemia in blast crisis (Bredella and Stoller, 2007).
**Ewing’s Sarcoma:**

Ewing’s sarcoma (ES), first described by James Ewing in 1921 as a diffuse endothelioma of bone, initially was believed to be of perivascular endothelial origin. Ewing's sarcoma is a primary malignant tumor of bone that is example of disorders that involve infiltration or replacement of normal marrow with tumor cells (*Volger III and Murphy, 1988*). Ewing's sarcoma is a highly malignant round cell neoplasm of uncertain origin (*El Khadrawy et al., 1999 and Bredella and Stoller, 2007*). Other authors suggested that Ewing's sarcoma originate from marrow stem cell, which is derived from the primary reticulum (*Yochum and Rowe, 1996*).

Recently, The Ewing’s sarcoma family of tumors (EFT) includes ES of bone (ESB), extraosseous ES (EES), peripheral primitive neuroectodermal tumor of bone (pPNET), and malignant small-cell tumor of the thoracopulmonary region, or Askin’s tumor; all of which are now known to be neoplasms of neuroectodermal origin. These tumors are characterized pathologically as small round blue cell tumors (*Carvajal and Meyers, 2005*).

Ewing sarcoma occurs during the second decade of life, making this tumor the second most frequent malignant bone tumor found in children and adolescents. ES has a predilection for boys (3:2 over girls) and is frequently found in the white population but rarely seen in other ethnic groups. ES occur most frequently in the long tubular bones and flat bones (scapula) in the appendicular skeleton, and the ribs and pelvis in the axial skeleton. Neoplasms of the long bones predominate in patients in the first two decades of life, whereas lesions of the flat bones are more prevalent in older patients. Only rarely is an ES located periosteally or in the epiphysis. ES most often occurs in the diaphysis of the proximal and mid-humerus, mid-femur, proximal and mid-tibia, and mid-fibula. Lesions may be found in the metaphysis, particularly in patients over 16
years of age (*Miller and Hoffer, 2001*).

Ewing’s sarcoma represents 3% of pediatric malignancies. Most patients present between 10 and 15 years of age, and 70% of cases present before age 20 years. Ewing’s sarcoma typically presents with localized pain and swelling with an associated soft tissue mass (*Gibbs et al, 2006*). Occasionally, joint effusions or neurologic symptoms are present. Development of systemic symptoms, including fever, malaise, weight loss, and leukocytosis, is generally indicative of metastasis and a fulminating course. Local recurrences and lung metastases are not unusual in a patient with an aggressive ES (*Miller and Hoffer, 2001*).
MR IMAGING OF BONE MARROW INFILTERATIVE LESIONS

General MR Features Of Marrow Infiltration Or Replacement:

The effect of different infiltrating processes on marrow signal patterns depends largely on the type of cells or tissues infiltrating the marrow and the degree of cellularity of the process. Other factors affecting the signal patterns include hemorrhage, necrosis, fibrosis, sclerosis, and inflammatory debris with associated water content or edema. Substantial overlap among these disorders exists. Therefore, histologic prediction based on MR findings is unreliable. Bone marrow biopsy is required to make that determination if necessary (Volger III and Murphy, 2006).

There are three MR pathologic patterns of abnormal marrow that reflect different types of histologic infiltration of the bone marrow (Vogler III and Murphy, 1988 and Moulopoulos et al., 1992). The focal pattern consists of localized areas of abnormal marrow. This pattern is often observed in metastatic disease from solid primary malignancies. On T1-weighted images, focal lesions are darker than yellow marrow and slightly darker or isointense to red marrow. On T2-weighted images they are brighter than both red and yellow marrow, and on enhanced T1-weighted images they enhance to various degrees depending on the vascularity of the underlying pathologic process. STIR and fat-saturation T2-weighted images provide increased contrast between focal lesions and uninvolved marrow (Moulopoulos and Dimopoulos, 1997).

In the diffuse MR pattern of abnormal marrow, the normal bone marrow is completely replaced by the abnormal process. The intervertebral discs appear brighter or isointense to the diseased marrow. This pattern is typical for the acute leukemias. On T1-weighted images, there is a diffuse decrease in the signal intensity of the marrow. In young
adults, a diffuse MR pattern may be difficult to differentiate from pure hematopoietic marrow on T1-weighted images. On T2-weighted images of diffuse patterns of marrow involvement, a variable increase in the signal intensity of the abnormal marrow is observed. This increase in signal may be difficult to appreciate because there is no normal marrow for comparison. After the administration of intravenous contrast, the abnormal marrow enhances. The intervertebral discs appear darker than the enhanced spine. The presence of enhancement is easily appreciated when direct comparison with the precontrast T1-weighted MR images is made (Moulopoulos et al., 1992 and Moulopoulos and Dimopoulos, 1997).

The variegated pattern consists of innumerable small foci of disease on a background of intact marrow. The small lesions of the variegated pattern are dark on T1-weighted images and bright on T2-weighted images, and they enhance after the administration of intravenous contrast (Moulopoulos and Dimopoulos, 1997).

With neoplastic infiltration of bone marrow, the common characteristics of high signal intensity on T2-weighted and STIR images and low signal intensity on T1-weighted images are similar to those of infection. MR imaging is very limited in evaluation of the lesional matrix, which is often key in determination of tumor type. However, MR imaging provides exquisite information regarding involvement of the surrounding compartments such as the soft tissues, adjacent joints, and neurovascular bundle. Neoplastic processes may be depicted as diffuse, patchy recruitment of the marrow spaces, discrete focal involvement, or diffuse and uniform (Andrews, 2000)

Diffuse or focal involvement of bone marrow with tumor may be due to plasma cell myeloma, leukemia, lymphoma, primary bone neoplasms or metastatic disease (Steiner et al., 1993).
Bone Marrow Metastases:

Algra et al., 1991 described four MRI patterns of metastases, focal lytic lesions usually demonstrate decreased signal on T1-weighted images and increased signal on T2-weighted images (or T2* gradient echo images) compared to normal marrow. Focal blastic lesions demonstrate decreased signal on both T1 and T2-weighted Images. Diffuse inhomogeneous or diffuse homogeneous patterns are the other two patterns (Figure 21).

Greenfield and Arrington, 1995 said that osteolytic metastases are the commonest type of metastases. Yochum and Rowe, 1996 also said that osteolytic metastases are represent approximately 75 percent of all metastatic lesions, osteoblastic metastases represent approximately 15 percent of all lesions, mixed lesions represent approximately 10 percent of all metastatic deposits.

The incidence of lytic, blastic, and mixed types of bone metastases is different in various tumor types. Lytic lesions may be seen in almost all tumor types. Bone metastases of bladder, kidney, and thyroid cancer and lesions of multiple myeloma are invariably lytic. Blastic lesions are frequently seen in prostate and breast cancer, occasionally in lung, stomach, pancreas, and cervix carcinomas, and infrequently in colorectal cancer (Padhani and Husband, 1998).
Review of literature

Figure (21): Diagram illustrates four basic patterns of metastases seen on MR images: osteolytic (focal areas of low signal intensity on T1-weighted images and high signal intensity on T2- or T2*-weighted images), sclerotic (focal areas of low signal intensity on both T1- and T2- or T2*-weighted images), diffuse inhomogeneous, and diffuse homogeneous. (Algra et al, 1991).
Many patients with bone metastases are asymptomatic and metastases are detected incidentally on routine screening or when a cause for rising tumor markers is looked for. Symptoms occur mainly when the lesion increases in size, causing extensive bone destruction, which may lead to collapse or fracture, or in the presence of accompanying complications, such as spinal cord compression or nerve root invasion (Even-Sapir, 2005).

MRI has good spatial and contrast resolution. It is an optimal imaging modality for bone marrow assessment. MRI can detect an early intramedullary malignant lesion before there is any cortical destruction or reactive processes. Normal marrow shows a high-intensity signal on T1-weighted imaging, whereas metastases appear as areas of reduced signal, reflecting the replacement of fat in the marrow by tumor. Bone marrow metastases have longer T1- and T2-weighted relaxation time than normal marrow and are usually enhanced after the administration of contrast medium. MRI can detect bone marrow metastases missed by bone scan (Even-Sapir, 2005).

Detection of malignant marrow infiltration by MRI is better than by CT. Moreover, MRI has a better contrast resolution for visualizing soft-tissue and spinal cord lesions and, thus, is superior to CT in differentiating benign and malignant causes of spinal cord compression and vertebral compression fracture (Karnholz R, Sze G., 1991). However, MRI is less sensitive than CT for detecting cortical bone destruction because cortical bone appears black on T1- and T2-weighted sequences (Vogler III and Murphy, 1998).

The specificity of MRI is moderate because of overlap in the appearance of metastases and a variety of benign lesions. In the vertebral column, for instance, benign lesions, which may be confused with metastases, include degenerative disk disease, osteomyelitis, a benign
compression fracture, infarcts, and Schmorl’s nodes. An abnormal signal in the posterior aspect of the vertebral body extending into the posterior elements suggests a malignant nature (Even-Sapir, 2005).

A metastatic bone or bone marrow lesion is defined on T1-weighted spin-echo images, as focal or diffuse hypointense bone marrow signal intensity relative to adjacent (or, in the extremities, contralateral) normal bone marrow. In patients older than 10 years, normal bone marrow was defined as hyperintense relative to adjacent skeletal muscle tissue, and neoplastic marrow was defined as hypo- or isointense to adjacent muscle tissue. In younger patients, the distribution of normal hematopoietic marrow should be considered in the assessment. When MRI is performed in young adults, highly cellular malignancy needs to be differentiated from hematopoietic marrow, which shows age-dependent variability (Daldrup-Link et al, 2001).

It might be difficult to differentiate between active disease and scar, necrosis, or fracture when monitoring the response to therapy by MRI. Currently, the use of MRI is mainly reserved for regional assessment of a bone lesion suggested by bone scan or CT (Vanel et al, 2000).

In the adult pelvis, the complex interaction of normal age-associated changes in bone marrow, physiologic reconversion, and metastatic deposition makes areas of low signal intensity on T1 weighted MR images of the pelvis difficult to interpret. Two signs are used to help interpret these suspect areas. The bull’s-eye sign and the halo sign. The bull’s-eye sign is a one or more foci of high signal intensity (equivalent to that of subcutaneous fat) within an area of low signal intensity on a T1-weighted image focus of an osseous lesion. It represents a focus of fat within islands of hematopoietic marrow. This was considered a negative predictor of metastasis. A positive halo sign consisted of a rim with high
signal intensity around a lesion with lower signal intensity on T2-weighted images. The halo sign occurs secondary to the destruction of trabeculae and thereby causes a fluid-filled gap that cause a relative increase in peripheral signal intensity on T2-weighted images. In addition, foci of new bone also seen in the periphery may contribute to the signal intensity. Halo signs are fairly sensitive and highly specific in identification of metastases (Figures 22 – 23) (Schweitzer et al, 1993).

On STIR images, Tumor deposits are typically hyperintense or bright and are conspicuous against a dark background of suppressed signal intensity within fat. The additive effects of prolonged TI and T2 relaxation times observed in most primary and secondary tumors result in dramatic signal hyperintensity at the site of metastatic deposits. Although osteoblastic metastases are less conspicuous than osteolytic lesions, they are easily identified as hyperintense foci surrounded by reactive hypointense sclerosis. Although osteoblastic metastases are readily identified on scintigraphy, the ability to discriminate reactive sclerosis from true metastasis on MR imaging appears to allow a more realistic evaluation of true tumor burden. In addition, osteoblastic activity reflecting an attempt at bone healing after chemotherapy (the flare phenomenon) may misleadingly suggest advancing disease on scintigraphy (Eustace et al., 1997).
**Figure (22):** TI-weighted MR image from a patient without metastasis. Two foci of low signal intensity (black arrows) in marrow in the left ilium are noted. Centrally, a bull’s-eye is seen. An incidental finding is a nutrient artery (white arrow) in the left ilium *(From Schweitzer et al, 1993)*

**Figure (23):** MR images from a patient with breast cancer metastases. (a) T1-weighted (500/18) image reveals subtle areas of low signal intensity in the anterior femoral head (large arrow, a and b) and anterior acetabulum (small arrow, a and b) without recognizable bull’s-eyes. (b) Halos around both lesions are seen on this T2-weighted (2,500/80) image *(From Schweitzer et al, 1993)*
Because the vertebral body has a relatively large marrow cavity, early or small metastases tend to be intramedullary lesions without cortical involvement and may not cause sufficient bony remodeling to be detected on bone scans. Small lesions or lesions localized away from the cortex are, therefore, likely to be undiagnosed on bone scintigraphy, despite destruction of trabecular bone. Even if most of the bone marrow has been infiltrated with metastases, the uptake of radioactive tracers caused by the destruction of the relatively small amount of medullary bony matrix remains low and, therefore, may not be easily appreciated when the uptake is contrasted with that of the normal cortex. Although MR imaging is useful in the detection of early metastases that are localized completely in the bone marrow cavity, bone scintigraphy remains the most cost-effective method for examination of the entire skeleton. MR imaging can be useful in cases in which bone scan findings remain negative and vertebral involvement is suspected on the basis of clinical findings. However, MR imaging is inadequate in assessing cortical involvement (Taoka et al., 2001).

Whole-body MR imaging is used by many authors for evaluation of bone marrow metastases. Early results suggest that the skeletal system of the entire body can be scanned within 30–45 min on turbo short tau inversion recovery (STIR) imaging and within 6 min with total body echo-planar imaging, and the detectability of metastatic tumor with these imaging techniques seems to be better than that with bone scintigraphy. However, turbo STIR imaging and total body echo-planar imaging are not widely used methods and are suboptimal for the metastatic workup of the entire skeletal system on classic MR sequences. MR imaging is not cost-effective in examining bones with small cavities such as ribs because it cannot globally examine the entire skeletal system as bone scintigraphy (Taoka et al., 2001).
Daldrup-Link et al, 2001 stated that Whole-body MR imaging has a higher sensitivity than skeletal scintigraphy for the detection of bone marrow metastases. Whole-body MR imaging has the potential to visualize the bone marrow (the initial site of neoplastic cell infiltration) directly and to determine abnormalities in bone marrow cell composition with high anatomic resolution. They examined 39 children and young adults. In smaller children, nine slabs with 9-15 slices each were acquired, which included head, thorax, abdomen, upper and lower spine, and the extremities. Slice orientation was coronal for the trunk and extremities and sagittal for the spine. In adolescents, upper and lower extremities were covered by two slabs each. To include both forearms in one slab, the arms were elevated above the head. The entire MR imaging procedure took 45 min in young children and 55-60 min in older children and adolescents. They performed both T1-weighted spin-echo and T2-weighted fat-suppressed short tau inversion recovery (STIR) imaging (TR/TE, 5420/29; flip angle, 180°) in the first 10 patients. In all subsequent patients, they performed spin-echo sequences only because the spin-echo images had a faster acquisition time (4 min per slab as opposed to 8 min per slab for STIR), showed fewer movement artifacts, had a higher spatial resolution, had a comparable sensitivity but higher specificity than STIR images in children. They found 21 patients to have bone metastases exhibited a total of 51 focal bone lesions. With analysis on a lesion-by-lesion basis, whole-body MR imaging showed a sensitivity of 82% for the detection of bone metastases, which was significantly higher than the sensitivity of 71% for skeletal scintigraphy.

Lauenstein et al., 2004 stated that on the basis of their study findings, whole-body MR imaging in less than 15 minutes is feasible for tumor staging. Whole-body MR imaging also provides good agreement with the conventional diagnostic methods for depicting metastases and
even proved to be more sensitive for hepatic and skeletal metastases than did the corresponding reference examinations. Three patients with osseous metastases at the Whole-body MR examination were determined to be free of osseous metastases at scintigraphy. Main discrepancies between scintigraphic and MR imaging findings were related to the anatomic region of osseous lesions: Whole-body MR imaging did not depict a considerable number of metastases in the skull and the ribs but depicted more lesions in the spine, the pelvis, and the femur.

MR imaging can help distinguish benign from pathologic compression fractures of vertebral bodies with conventional SE sequences. In general, chronic benign compression fractures are characterized by homogeneous isointense SI, compared with that of normal vertebral bodies on T1-weighted and fat images, as well as T2-weighted, water, and STIR images. Acute benign fractures demonstrate inhomogeneous low SI on T1-weighted and fat images and corresponding inhomogeneous high SI on T2-weighted, water, and STIR images. In contrast, pathologic fractures show homogeneous replacement of vertebral marrow with low SI on T1-weighted images; absent SI on fat images; and high SI on T2-weighted, water, and STIR images. Of the sequences depicting the disease as an area of high SI, the STIR sequence had the highest Contrast. Pathologic fractures are accompanied by diffuse rather than focal SI abnormalities in the vertebral body, results reflecting almost complete marrow replacement by tumor. This is probably a condition necessary for compression fracture to occur. The convex anterior and posterior contours of the compressed vertebrae are additional features that favor pathologic fracture (Baker et al., 1990).

The use of chemical shift MR imaging in bone marrow to distinguish benign from malignant processes has been reported in the axial skeleton. Zampa et al., 2002 evaluated 86 lesions by using T1-
weighted spin-echo and an out-of-phase gradient recalled echo MR imaging sequence to obtain out-of-phase images. Quantitative analysis consisted of a signal intensity ratio that was expressed by comparing the signal intensity of the lesion on out-of-phase images with the signal intensity of the lesion on conventional T1-weighted images (ie, signal intensity on out-of-phase gradient recalled echo MR images divided by signal intensity on T1-weighted spin-echo MR images). A cutoff value of 1.2 resulted. Lesions with values that were higher than the cutoff value were considered neoplastic, whereas lesions with values that were lower than the cutoff value were considered benign.

Zajick Jr et al., 2005, obtained another cutoff value similar to cutoff value by Zampa et al., 2002 but was calculated as a percentage, (ie, 20% decrease in signal intensity). In normal marrow and benign lesions have characteristic behavior at chemical shift MR imaging (ie, a consistent loss of signal intensity), while metastatic lesions tend to have different behavior at chemical shift MR imaging (ie, slight [if any] loss of signal intensity). on chemical shift MR images, there is a threshold cutoff value for the decrease in signal intensity. Any lesion that is not composed of fat on T1-weighted images and that loses less than 20% of its signal intensity on out-of-phase images compared with in-phase images should be considered suspicious for malignancy.

**Plasma cell dyscrasias:**

Plasma cell neoplasms are a group of diseases in which proliferation and accumulation of immunoglobulin-secreting cells occur in the bone marrow and in which a monoclonal protein is generally detected in the blood and/or in urine (Vande Berg et al., 1998c). Ambrosino et al., 1992 mentioned that multiple myeloma is the most common of the plasma cell dyscrasias. It is also the most common primary bone tumor in adults (Brown, 1993, Amour et al., 1994 and Bredella and Stoller, 2007).
**Multiple myeloma:**

Conventional radiographs of the skeleton are routinely obtained during the work-up of patients with suspected myeloma. Abnormal skeletal radiographs are detected in >80% of patients. The presence and number of punched-out lytic bone lesions formed the basis of the clinical staging system introduced in 1975 by Durie and Salmon. The presence of multiple lytic lesions places the patients in stage III. As many as 70% of patients with multiple myeloma are classified as having stage III disease, but this group is heterogeneous with survival ranging from a few months to several years. According to the Durie and Salmon staging system, absence of bone lesions on plain radiographs is associated with a lower stage and improved survival. However, the prognostic value of radiographic findings may be controversial, and in some series patients with skeletal surveys that appeared normal actually had a worse prognosis than patients with minimal lytic changes (*Moulopoulos et al., 2005*).

In recent years a number of readily available and easily reproducible laboratory variables have emerged as important prognostic factors for patients with multiple myeloma. In an attempt to circumvent the shortcomings of the Durie and Salmon staging system, the International Myeloma Working Group recently proposed an International Staging System (ISS) for multiple myeloma which is based on serum albumin and β2-microglobulin (*Moulopoulos et al., 2005*).

The initial imaging work up usually follows confirmation of the diagnosis based on typical laboratory findings and results of bone marrow aspiration. The newest International Staging System (*Table 1*) relates prognosis and survival solely to levels of beta 2 microglobulin and albumin introduced by Greipp et al; (2005), meant to predict prognosis, but does not incorporate imaging studies in its classification scheme. Treating physicians still find imaging information valuable in the care of
these patients and continue to depend on imaging studies for clinical decision making. Radiologists therefore should report their imaging findings with the Durie/Salmon PLUS staging system (Durie et al; 2003). D/S PLUS staging system (Table 2) is the 2003 update of the original 1975 D/S staging system proposed by Durie and Salmon, 1975.

Mulligan and Badros, 2007, stated that Durie/Salmon PLUS staging system (D/S PLUS) incorporate advanced imaging findings and radiographic bone survey findings as follows:

Imaging Stage I.
Zero-four focal bone lesions and/or mild diffuse spine disease on MR imaging. “Mild diffuse spine disease” is not defined, but can be deduced as anything less than “moderate diffuse spine disease.”

Imaging Stage II.
Five to 20 focal bone lesions and/or moderate diffuse spine disease by MR imaging. “Moderate diffuse spine disease” is defined as diffuse abnormality with the overall signal intensity of involved vertebral bodies, on T1-weighted sequences, brighter than the adjacent intervertebral discs.

Imaging Stage III.
More than 20 focal bone lesions and/or severe diffuse spine disease by MR imaging. “Severe diffuse spine disease” is defined as diffuse abnormality with the overall signal intensity of involved vertebral bodies, on T1-weighted sequences, equal to or less than the adjacent intervertebral discs.

Table (1): International staging system (Greipp et al; 2005)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Laboratory values</th>
<th>Average survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum beta2-microglobulin &lt;3.5 mg/l Serum albumin ≥3.5 g/dl</td>
<td>62 months</td>
</tr>
<tr>
<td>II</td>
<td>Not meeting criteria for stage I or stage III</td>
<td>44 months</td>
</tr>
<tr>
<td>III</td>
<td>Serum beta2-microglobulin ≥5.5 mg/l</td>
<td>29 months</td>
</tr>
</tbody>
</table>
Table (2): Durie/Salmon PLUS staging system for symptomatic multiple myeloma (*Durie et al; 2003*)

<table>
<thead>
<tr>
<th>Stage I clinical criteria</th>
<th>&lt;5 focal lesions ± mild diffuse spine disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II clinical criteria</td>
<td>5–20 focal lesions ± moderate diffuse spine disease</td>
</tr>
<tr>
<td>Stage III clinical criteria</td>
<td>&gt;20 focal lesions ± severe diffuse spine disease</td>
</tr>
</tbody>
</table>

Imaging is important in the diagnosis of multiple myeloma. Nuclear scintigraphy using technetium is limited and there must be significant medullary bone involvement before osteoporosis or lytic lesions can be detected on conventional radiographs. MR imaging is well suited to demonstration of marrow involvement, which is characteristically multifocal. Multiple myeloma may also present as a complete marrow replacement, simulating leukaemia (*Bredella and Stoller, 2007*).

MR evaluation of multiple myeloma includes the following: Areas of involvement demonstrate low signal intensity on T1-weighted images and high signal intensity on T2-weighted, STIR, and Gd-DTPA enhanced images. STIR images demonstrate greater lesion contrast than that seen on corresponding conventional T2-weighted images. Whole-body imaging is useful in detecting the extent of myelomatous involvement. The percentage of bone marrow involvement may not correlate with the MR appearance, however (*Bredella and Stoller, 2007*).

MRI is a qualitative measure, i.e. the degree of marrow infiltration by bone marrow biopsy and the degree of hyperintensity on STIR sequence may be difficult to correlate. T₁-weighted MR images are most sensitive in depicting abnormal bone marrow. In patients with focal bone marrow patterns, MRI may reveal lesions as small as 5 mm but it may not
show microscopic disease. In patients with the diffuse MRI pattern the change in signal intensity depends on the percentage of neoplastic cells in the bone marrow, i.e. bone marrow plasmacytosis below 10% may be associated with a false-negative MRI study (Moulopoulos et al., 2005).

MR imaging findings in MM closely reflect the broad spectrum of pathologic tumoral spread. The distribution of malignant plasma cells in MM includes sites that show normal areas of active hematopoiesis in adults. These are in the bone marrow of the axial skeleton. The combination of the diagnostic accuracy afforded by current MR units and the extensive coverage by phased-array spine coils allows the acquisition of survey studies of long segments of the axial skeleton within a reasonable time period (Mulligan and Badros, 2007).

In general, MR imaging in MM is identified as hypointensities on T1-weighted images, hyperintensities on STIR images, and enhancement on gadolinium-enhanced images. These imaging features are not pathognomonic for MM and may also be seen in other diseases that affect the marrow. In general, however, MM is suspected whenever MR images depict an expansile focal mass; multiple focal masses in the axial skeleton; diffuse marrow involvement, particularly at known sites of normal hematopoiesis; or multiple compression fractures in a patient with no known primary malignancy (Edgardo et al; 2004). Each typical focal lytic lesion seen with any imaging method is counted as an individual abnormality, and the total number of lesions is summed to fit with the appropriate stage in the D/S PLUS system (Mulligan and Badros, 2007).

Multiple myeloma exhibits nonspecific changes on T1-weighted images and therefore can be difficult to distinguish from normal marrow. Detection of bone marrow myeloma is best achieved with STIR or T2-weighted images with fat suppression (Rahmouni et al; 1993a).
On these pulse sequences, untreated lesions are characterized by increased signal intensity. Untreated lesions also routinely show enhancement on T1-weighted images after the administration of gadolinium. However, this feature does not improve T1-weighted image detection of myelomatous lesions as compared with T2-weighted or STIR images (Rahmouni et al; 1993b).

In patients with newly diagnosed MM, low tumor burden is normally associated with a normal MR pattern. On the other hand, high tumor burden is suspected when marrow is diffusely hypointense on T1-weighted images, hyperintense on STIR images, and enhancing on gadolinium-enhanced images. Overall marrow signal intensity may be homogeneous or heterogeneous. Findings of diffuse marrow involvement may also be appreciated in a setting of increased hematopoiesis in patients with severe anemia or in states of marrow repopulation, which are usually drug induced (stimulation with growth factors) (Angtuaco et al; 2002).

Lytic bone lesions or demineralization occur at presentation in more than 80% of patients with multiple myeloma. Radiographic bone surveys have been part of the staging system for multiple myeloma for the last 20 years. However, it should be recognized that, when a lytic lesion becomes evident on a conventional bone radiograph, more than 50% of bone loss has occurred (Moulopoulos and Dimopoulos, 1997). In a study by Staebler et al, 1995, 55% of patients with focal MR patterns of multiple myeloma and 50% of patients with diffuse MR patterns of multiple myeloma did not have lytic lesions on bone radiographs. The range of abnormal MR studies in patients with multiple myeloma varies from 50% for patients with indolent disease to 100% for patients with symptomatic disease.
All three MR patterns of abnormal marrow have been observed in patients with multiple myeloma (Moulopoulos et al., 1992, Rahmouni et al., 1993 and Moulopoulos et al., 1995). The focal lesion pattern is more frequently observed than the other two and is more often associated with lytic lesions on bone radiographs. It is interesting to note that, in a recent series, only 12 (18%) of 66 focal myelomatous lesions on spinal MR images had corresponding lytic lesions on skeletal surveys (Moulopoulos et al., 1992). The increased incidence of positive bone surveys in patients with focal MR patterns can be attributed to focal growth of dense plasma cell aggregates that produce local bone destruction (Moulopoulos and Dimopoulos, 1997).

Diffuse marrow involvement occurs in 25% of patients with multiple myeloma. This pattern has been associated with lower hemoglobin values and higher percentages of bone marrow plasmacytosis. The association of the diffuse MR pattern with more advanced disease supports an earlier report of a shorter survival rate for patients with multiple myeloma and negative bone radiographs (Moulopoulos et al., 1992). In that study, Smith et al., 1988, proposed that a more diffuse involvement of the bone marrow may account for the poor prognosis of their patients with negative skeletal surveys. Correlation of the levels and the activity of several cytokines (interleukin-6, interleukin-1α, tumor necrosis factor, etc, which are implicated in the process of bone destruction in myeloma) with the MR patterns of multiple myeloma may help explain the different fashions of spread of the disease. Before the prognostic significance of the MR patterns of marrow involvement in myeloma is established, further studies with a long-term follow-up need to be performed (Moulopoulos and Dimopoulos, 1997).
Approximately 15% of patients who have multiple myeloma are free of symptoms when diagnosis is made after screening examinations show increased serum protein levels or mild anemia. Patients with asymptomatic, low tumor mass myeloma are observed without treatment until there is evidence of disease progression (Dimopoulos et al., 1993). A prospective study with 38 patients with asymptomatic myeloma of low tumor mass and negative skeletal surveys showed that 19 (50%) patients had evidence of marrow involvement on spinal MR images (Moulopoulos et al., 1995).

A similar analysis by Vande Berg et al., 1996 and 1997a showed involvement of the bone marrow on MR images in 29% of patients with stage I myeloma and in 19% of 35 patients with monoclonal gammopathy of undetermined significance (MGUS). The same investigators observed 37 patients with MGUS for a mean of 31 months: 4 of 7 patients with abnormal MR studies at diagnosis and none of 30 patients with normal initial MR studies showed evolutive disease at follow-up. Abnormalities on MR images and the presence of Bence Jones protein in the urine were the only two parameters predictive of disease progression. Even when the tumor burden is very low, MR imaging may detect occult foci of myelomatous involvement and may predict a more precarious course of the disease.

Moulopoulos and Dimopoulos (1997) described a variegated marrow appearance on T1-weighted images, suggestive of scattered focal nodular deposits of plasma cells. Angtuaco et al; 2004 stated that MM are usually multiple and highly variable in distribution, with the majority located in the thoracic and lumbar spine and the pelvis. They range from small to large expansile focal masses. Focal lesions with diffuse marrow involvement may coexist.
Regardless the pattern of involvement, myeloma almost always have signal intensity equal to or lower than skeletal muscle or disc on T1-weighted images, which may be somewhat difficult to distinguish from normal red marrow. Occasionally, focal lesions will have high signal intensity on T1 WI, presumably from hemorrhage into the lesion (Kaplan and Dussault, 1997). On T2W 1, the myelomatous lesions demonstrate increased signal intensity (Fruehwald et al., 1988 and Libshitz et al., 1992).

Spinal compression fractures occur in 55%–70% of patients with MM (Lecouvet et al; 1997). The spine is a common site of involvement by myeloma due to the presence of red marrow in the axial skeleton throughout life. Imaging of a patient with known myeloma and suspected spinal cord compression should be performed emergently as the disease may progress rapidly. MR imaging can help distinguish benign from malignant compression fractures. A benign osteoporotic fracture is suggested when a retropulsed bone fragment is seen, when fat signal is preserved on T1-weighted images throughout the body and there is no high signal on T2-weighted images, when there is only a thin (<1 cm) surrounding soft tissue component and when horizontal band-like areas representing the fracture plane are seen following gadolinium administration. A malignant etiology of collapse is suggested when the posterior cortex is convex towards the spinal canal, epidural mass is seen, when the entire vertebral body or pedicles are replaced by low signal on T1-weighted images, and high or heterogeneous signal is seen within the body following gadolinium injection or on T2-weighted images (Mulligan and Badros, 2007).

The combination of T2-weighted and gadolinium-enhanced T1-weighted images holds promise for evaluation of response to therapy. Based on small numbers of patients, patterns of therapeutic response
include nonenhancing or rim-enhancing lesions. In non-responders there is no change in the pretreatment enhancement pattern or in the T2-weighted signal intensity of the lesions (Rahmouni et al; 1993b).

Whether used to evaluate treated or untreated patients, MRI are currently the most sensitive imaging method available for detection of myelomatous marrow involvement. MRI of patients with myeloma demonstrates marrow involvement even when radionuclide bone scans and conventional radiographs are normal. Despite this, some patients with known myeloma will have normal MR studies. MRI has been shown to demonstrate evidence of marrow involvement in 25% to 50% of patients with stage I disease (Salmon and Durie classification) and 80% of myeloma patients with stage III disease (Moulopoulos and Dimopoulos 1997, Vande Berg et al; 1996 and vande Berg et al; 1997a). The remainder of patients in both groups will display normal MR studies. Stage I patients with abnormal marrow on MRI appear to have a shorter time interval before more aggressive disease develops than stage I patients with normal MR studies (Moulopoulos and Dimopoulos 1997 and Vande Berg et al; 1997a).

In stage III myeloma, the presence of focal or diffuse spinal marrow disease patterns on pretreatment MR studies is an indicator of a poor response to induction of chemotherapy (Lecouvet et al; 1998). Those stage III patients with diffuse spinal marrow disease have more severe alterations in hematologic parameters than patients with focal patterns or normal marrow. Also, patients with stage III myeloma and diffuse marrow involvement or greater than 10 lesions on MR studies show an increased risk (six times) for developing compression fractures than do stage III patients with normal MR marrow patterns or less than 10 foci of disease. Those patients with stage III disease and an abnormal MR appearance of spinal marrow who elect not to undergo therapy show
shorter survival than patients with normal MR spinal studies ([Lecouvet et al; 1998]).

MR findings in multiple myeloma patients who have responded to chemotherapy include: Resolution of the abnormal marrow or a persistent marrow abnormality without associated contrast enhancement is seen in a positive therapeutic response. A pattern of peripheral rim enhancement also correlates with a positive response to chemotherapy. A partial response to treatment is characterized by conversion from a diffuse to a variegated or focal marrow pattern, with decreased signal intensity in areas of marrow previously showing persistent contrast enhancement with intravenous gadolinium ([Bredella and Stoller, 2007]).

**Plasmacytoma:**

**Major et al; 2000,** stated that solitary plasmacytoma appears in MRI as expansile lesions, which had low signal intensity on T1-weighted images and high signal intensity on T2-weighted images involving the entire vertebral body. The lesion had curvilinear low-signal-intensity structures on all imaging sequences that extended partially through the vertebral body and resembled sulci seen in the brain, which they termed a "mini brain" appearance on axial images. This "mini brain" appearance is pathognomonic of plasmacytoma of the spine on MR imaging. These low-signal-intensity structures that resembled the sulci in brain are likely caused by thick cortical struts seen in plasmacytoma. The cortical thickening in the arrangement of plasmacytoma appears to be unique to this tumor. This appearance can also be seen on CT of plasmacytoma.

A mini brain appearance in an expansile lesion of the vertebral body is sufficiently pathognomonic of solitary plasmacytoma. It is important to appreciate this finding because it may help radiologists recommend appropriate laboratory studies and facilitate early and appropriate treatment. For the patient, an early diagnosis on MR imaging
may obviate biopsy. Although a biopsy may still be required at many institutions, our surgeons consider this finding sufficiently pathognomonic to avoid biopsy before treatment (Figures 24-25) (Major et al; 2000).

Many tumors involving the axial skeleton can be expansile, have low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, and involve the entire vertebral body. These imaging characteristics are nonspecific, however the appearance of a mini brain on axial images is characteristic of plasmacytoma (Major et al; 2000).

The characteristic appearance of thickened cortical struts is probably a result of a stress phenomenon from the lytic process of the plasmacytoma forcing the remainder of the bone to increase thickness as a compensatory response to weakening bone. Perhaps an explanation of this appearance, which is not seen in other primary bone or metastatic spine lesions, concerns the less aggressive nature of plasmacytoma compared with other tumors that destroy bone. The cortical thickening in the arrangement of plasmacytoma appears to be unique to this tumor (Major et al; 2000).

This appearance can also be seen on CT of plasmacytoma (Helms and Genant, 1988). The CT appearance of Paget's disease and hemangioma is also reported to have thickening of the remaining trabecular bone (Helms et al, 1985). However, the appearance of hemangioma and Paget's disease on MR imaging does not produce the mini brain appearance, and the signal characteristics are not predictably low on T1-weighted images and high on T2-weighted images (Major et al; 2000).
Figure (24): A 37-year-old woman with back pain. Axial fast spin-echo T2-weighted MR image shows abnormal high signal intensity throughout vertebral body and linear low signal intensity resembling sulci of brain “mini brain appearance” (Major et al; 2000).

Figure (25): 37-year-old woman with back pain. A, T1-weighted sagittal MR image through thoracic spine shows diffuse low signal intensity replacing T7 vertebral body. B, Corresponding fast spin-echo T2-weighted MR image with fat suppression shows high signal intensity throughout vertebral body with linear low signal intensity struts that represent cortical thickening “mini brain appearance” (Major et al;
**Lymphoma:**

*Guermazi et al; 2001* stated that in Hodgkin’s disease, bone marrow involvement is rare at presentation; consequently, marrow biopsy is not systematically indicated as part of initial staging. During the course of illness, 5%–32% of patients will develop bone marrow involvement. When tumor infiltration is seen at imaging, clinical stage IV disease is presumed. Hodgkin disease is more likely to form focal lesions. Osseous involvement occurs in 5%–20% of patients during the course of Hodgkin disease but is seen in only 1%–4% at presentation. Primary bone Hodgkin disease probably does not exist. Osseous involvement may result from either contiguous spread or a hematogenic process that is usually a late manifestation. The bone lesions are found in the following locations (in decreasing order of frequency): dorsolumbar spine, pelvis, ribs, femora, and sternum. Limb and cervical involvement are rare. Focal extension from adjacent lymph nodes does not alter staging.

**Primary lymphoma of bone:**

Primary lymphoma of bone is characterized by lymphomatous involvement of the medullary cavity of a single bone, without concurrent lymph node or visceral involvement, for at least 6 months. It is important to differentiate primary lymphoma of bone from skeletal involvement in systemic lymphoma, since it has a better prognosis and is treated differently than systemic lymphoma (*Bredella and Stoller, 2007*).

Primary lymphoma of bone manifests with insidious and intermittent bone pain that can persist for months. Other signs and symptoms include local swelling, a palpable mass and systemic symptoms such as weight loss and fever. Vertebral involvement can cause radicular symptoms and can even lead to compression of the spinal cord (*Krishnan et al; 2003*).
MR imaging is a noninvasive technique that can assess the status of large volumes of bone marrow. In patients with lymphoma, MR imaging has been shown to be superior to bone marrow scintigraphy in the evaluation of the bone marrow (Moulopoulos and Dimopoulos, 1997).

Unlike leukemia, lymphoma tends to form nodules or marrow tumors, although at times it is diffuse and simulates leukemia on MR images. When diffuse, it can usually be detected by posterior crest marrow biopsy. Frequently, however, sampling error produces a negative marrow biopsy finding, especially when lymphomatous involvement is asymmetric. Bone scanning results are also frequently negative, even in lymphoma patients with known marrow involvement (Bredella and Stoller, 2007).

MR imaging, however, has the advantage of being able to sample a large volume of marrow, thus making it possible to detect marrow involvement. Since identification of marrow tumor in patients with lymphoma affects both staging and treatment, this is potentially one of the more important clinical applications for MR imaging of the body (Bredella and Stoller, 2007).

Shields et al; 1987 reported positive biopsy results in 10% and positive results with scintigraphy in 29% and with MR images in 39% of 38 patients with Hodgkin's disease. They concluded that MR imaging combined with histologic examination of the bone marrow improves the evaluation of the bone marrow status and the staging of lymphoma.

Smith et al; 1995 found marrow involvement on the MR images of one third of their patients with lymphoma who had negative bone marrow biopsies. Tsunoda et al; 1997 detected abnormalities in 52% of 56 patients with lymphoma who underwent MR imaging of the femoral marrow. Among patients with negative marrow biopsies (69%), a significantly poorer survival was shown for those patients with abnormal
MR studies of the femoral marrow compared with patients with normal MR studies. The diagnostic yield of the bone marrow biopsy can be increased if the biopsy site is selected with the aid of MR images. Nevertheless, if marrow involvement is shown on skeletal MR images of patients with lymphoma, a clinical stage IV should be assigned to the patient. MR images can also direct harvest procedures for autologous bone marrow transplantation to sites of relatively uninvolved marrow (Moulopoulos and Dimopoulos, 1997).

On T1-weighted MR images, lymphomatous involvement of the bone marrow is seen as diffuse, primarily heterogeneous replacement of the marrow and less frequently as focal marrow lesions. On T2-weighted images, the signal of the abnormal marrow increases and on T1-weighted images after the intravenous administration of contrast, the abnormal marrow enhances. The MR patterns of lymphomatous involvement of the bone marrow may be indistinguishable from similar patterns in myeloma, leukemia, and other malignant or benign diseases of the bone marrow. MR imaging cannot differentiate between the different histologic subtypes of lymphoma (Moulopoulos and Dimopoulos, 1997).

Krishnan et al; 2003 described Bone Marrow Replacement in primary bone lymphoma as follows: T1-weighted pulse sequences are the best (compared with other sequences) for demonstrating marrow changes, as T1-weighted images reveal areas of low signal intensity within the marrow. On T2-weighted images, these areas generally appear bright. Peritumoral edema and reactive marrow change can also produce high signal intensity on T2-weighted images. However, if fibrosis is present in a lesion, it may show low signal intensity. STIR (short-inversion-time inversion recovery) images, which are obtained with heavily T2-weighted pulse sequences, similarly delineate the normal from abnormal marrow.
When contrast material is administered, MR images can demonstrate areas of enhancement within the lesion.

**Soft tissue involvement in MRI:**

*Krishnan et al; 2003* stated that soft tissue involvement was observed in nearly all their cases that had a permeative pattern on plain radiographs were associated with soft-tissue masses on MR images. Interestingly, the pattern of extensive marrow disease and surrounding soft-tissue masses but without extensive cortical destruction has been reported nearly exclusively in round cell tumors such as primary bone lymphoma, multiple myeloma, and Ewing sarcoma. One explanation for this finding is the spread of tumor cells from the marrow through small vascular channels that run through the cortex into the surrounding soft tissue.

Its superior contrast resolution compared with CT makes MR imaging the modality of choice for the demonstration of soft tissue involvement. *Moulopoulos and Dimopoulos, 1997* have observed that extraosseous tumor in patients with lymphoma often occurs without obvious destruction of the cortical bone, reflecting the permeative nature of the tumor. MR images may show extensive involvement of the marrow and extraosseous soft tissues, with tumor "wrapped" around an apparently intact bony cortex (*Vourtsi et al., 1997*). On bone radiographs and on CT, the involved bones may appear normal. This characteristic appearance of the extraosseous extent of lymphomatous involvement of the bone marrow is not pathognomonic for this disease and may be observed in other malignancies, particularly those of small cell origin. However, its
presence may raise the possibility of lymphoma and direct the appropriate work-up. Caution should be taken to avoid misdiagnosing retroperitoneal lymphadenopathy for bone marrow involvement with extrasosseous extension of tumor (Moulopoulos and Dimopoulos, 1997). Recently, Fenstermacher et al., 1999, reported a 100% accuracy in the diagnosis of primary lymphoma of the bone versus osteosarcoma and Ewing sarcoma when no cortical destruction was detected in the area of bone marrow involvement and soft-tissue mass.

**Prognostic significance of MRI:**

To determine the clinical and prognostic significance of magnetic resonance imaging (MRI) of the femoral marrow in patients with malignant lymphoma Tsunoda et al; 1997 evaluated 56 patients with newly diagnosed lymphoma including 48 with non-Hodgkin's lymphoma (NHL) and 8 with Hodgkin's disease. MR images of the femoral marrow were obtained by the T1-weighted spin echo method and the short TI inversion recovery technique. Abnormal "positive" images were seen in 29 of the 56 patients (52%). All 17 patients with positive biopsy results showed abnormal images on their femoral marrow MRI. Three "positive" MRI patterns — scattered (72%), uniform (21%), and nodular (7%) — were observed. The overall survival of the patients with a positive MRI pattern was significantly poorer than that of patients with a normal pattern. Survival did not differ significantly according to MRI pattern. The 3-year survival rate in the patients with a normal MRI pattern was 89.9% and in the patients with a positive MRI pattern, it was 41.0%. This difference was statistically significant (P = .0279) when they evaluated only the patients with NHL. Patients with positive MRI patterns, but a normal bone marrow histology, showed a significantly shorter survival than those with a normal MRI pattern (P = .016). These results indicate that abnormal MR images of the femoral marrow are associated with a
significantly poorer survival in patients with malignant lymphoma, regardless of histologic findings in the marrow.

**Primary Multi-focal Osseous Lymphoma.**

The criteria for a diagnosis of primary bone lymphoma initially suggested by *Coley in 1950* with minor modifications are as follows: "lymphoma presenting in an osseous site with no evidence of disease elsewhere for at least 6 months after diagnosis." The presence of regional lymph node involvement does not exclude a diagnosis of primary bone lymphoma, but histologic confirmation of the diagnosis is necessary (*Krishnan et al; 2003*).

Primary Multi-focal Osseous Lymphoma is a radiographic subtype of lymphoma in which more than one bone is affected. Although the original criteria of *Coley* implied the involvement of a solitary bone, an expansion was suggested by *Ostrowski et al; 1986* when they attempted to subclassify osseous lymphoma into four groups. In their classification, group 1 consisted of solitary primary bone lymphoma, and group 2 encompassed cases in which more than one bone was affected but no nodal or visceral disease was present. (Groups 3 and 4 included cases with distant nodal or visceral disease.) The difficulty and controversy with the multifocal involvement discussed by *Ostrowski et al* is in distinguishing the cases with multiple osseous sites (ie, group 2) from those with disseminated disease (ie, groups 3 and 4), which would effectively exclude them from being called primary bone lymphomas. As a result, some authors do not consider multifocal osseous lymphoma at all, whereas others may have excluded it from their studies. Authors who support the concept have observed that multifocal osseous lymphoma has a predilection for bones around the knee, similar to the pattern of solitary primary bone lymphoma. In fact, as suggested by *Melamed et al; 1997*, the combination of scintigraphic abnormalities in the proximal tibia, distal
femur, and skull is very uncommon in metastatic disease and may, therefore, suggest the diagnosis of primary multifocal osseous lymphoma (Krishnan et al; 2003).

**MRI assessment of therapy in bone lymphomas:**

*Stroszczynski et al; 1999* investigated the value of MRI and $^{67}$Ga scintigraphy after therapy of bone lymphomas. They included both primary lymphoma of bone and secondary involvement of bone by extraosseous non-Hodgkin's lymphoma and Hodgkin's lymphoma in their investigation. They found that $^{67}$Ga scintigraphy had a sensitivity of 70% and a specificity of 93% for evaluating tumor activity. Dynamic contrast-enhanced MRI had a sensitivity of 90% and a specificity of 80%. The standard of reference was based on clinical, radiologic (radiography, CT, and bone scintigraphy), and histologic data. *Yuki et al; 2000* described a case of primary lymphoma of bone in complete remission, monitored with $^{67}$Ga citrate, $^{99m}$Tc hydroxymethylene diphosphonate, and $^{201}$Tl scintigraphy and MRI. Gallium-67 citrate scintigraphy reflected the change in tumor activity very rapidly, whereas bone marrow signal abnormalities persisted on MRI after six cycles of chemotherapy. *Melamed et al.; 1997* investigated multifocal primary lymphoma of bone in five patients with MRI after treatment. Despite a clinical report of complete remission, the authors described progression of most of the lesions on MRI. They did not describe the MRI criteria of progression and the type of therapy used in these patients (*Mengiardi et al; 2005*).

In their study *Mengiardi et al; 2005* described follow up of 25 patients with bone lymphoma under chemotherapy. They stated that tumor volume decreased in a pronounced fashion during the first 3 months after initiation of therapy and was reduced by 71-96% after 5 months with one exception. In this case, the MRI pattern during and after chemotherapy was similar to that of bone infarction. After 18-25 months,
only residual bone marrow abnormalities with 1-2% of the original tumor volume were seen. Parallel to the fast volume reduction, the soft-tissue component disappeared within a few months after the start of chemotherapy. In one patient, they observed incomplete disappearance of the soft-tissue component (≤ 15 months). This patient later presented with a distant recurrence. Although this finding is based on a single case, partial persistence of a soft-tissue component may represent a predictor for poor therapy response. On the basis of this data, they suggest performing MRI for monitoring at 2-3 months and 6-12 months after the start of therapy.

Mengiardi et al; 2005 also stated that signal characteristics of primary lymphoma of bone before treatment were non characteristic and uniform. During treatment, signal intensities and pattern of enhancement were not altered. Necrotic areas (as diagnosed on the basis of MRI criteria) were rarely observed before and during therapy. In two patients in whom histologic examination of the bone marrow abnormalities was available during therapy, necrosis and inflammatory changes were seen microscopically. Such findings underline the fact that MRI signal abnormalities may not differentiate bone marrow abnormalities after treatment from an active neoplasm (Figure 26).
Figure (26): 20-year-old woman with primary lymphoma of bone in proximal metaepiphysis of tibia and development of infarction like pattern after therapy. A, Coronal T1-weighted image reveals hypointense homogeneous tumor mass (white arrowheads) with focal destruction of medial cortical bone and small soft-tissue component (black arrowheads). B and C, Coronal T1-weighted (B) and coronal proton density–weighed fat-saturated (C) images obtained 10 months after start of therapy show pattern similar to that found in bone infarction with linear peripheral hypointense rim (arrows, B) on T1-weighted images and partial hyperintensity (arrows, C) on proton density–weighted image (From Mengiardi et al., 2005).
Leukemia:

MR imaging is the most effective means of visualization of bone and marrow involvement in acute leukemias. Whereas acute myelocytic leukemia infiltration is patchy, acute lymphoblastic leukemia is more diffuse. Leukemia should be considered when there is involvement of an entire bone or a neighboring bone with low signal on T1-weighted images or high signal on T2-weighted or STIR images (Miller and Hoffer; 2001).

Leukemias originate from clonal expansions of immature and mature white blood cell lines. Despite a common origin, they represent a heterogeneous group of infiltrative disorders with varying clinical and MRI features. Leukemic infiltration of marrow can be diffuse or spotty, depending on the extent of disease. MR studies of femoral marrow at the time of diagnosis in adults with acute leukemia typically identify uniform (41%), faint (31%), and scattered (28%) patterns of involvement (Takagi et al; 1995).

Marrow involvement in acute leukemia is typically diffuse and is characterized by monotonous infiltration of immature cells in a hypercellular marrow. In occasional cases of myeloblastic leukemia, particularly in very old patients, the marrow is normocellular or even hypocellular. Leukemic expansion in the marrow may elicit symptoms of skeletal tenderness or swelling of the larger joints. Transverse radiolucent bands involving the metaphyses can be seen in 40% to 53% of patients with acute lymphocytic leukemia. These “leukemic lines” represent leukemic infiltrates (Bredella and Stoller, 2007).

In the axial skeleton, because of the presence of larger red marrow fractions, distinct patterns are difficult to recognize. The most common MR finding observed in vertebral leukemic marrow is prolongation of TI relaxation values, resulting in an overall lowering of marrow signal
intensity on T1-weighted images. This usually results in signal intensities of the vertebral marrow appearing lower than that of intervertebral discs on T1-weighted images. Almost three fourths of patients with acute myeloid leukemia and nearly all patients with acute lymphoid leukemia have been shown to demonstrate this finding (Volger III and Murphy, 2006).

There is a demonstrated difference between measured T1 relaxation values of affected marrow in patients with newly diagnosed and/or relapsed leukemia as compared with affected marrow in patients in remission or in unaffected marrow in normal age-matched control subjects. A measured T1 value less than 600 ms correlates with a disease-free state, whereas a T1 value greater than 750 ms correlates with leukemia (newly diagnosed or in relapse) (Moore and Sebag, 1989).

Chemical shift imaging and proton spectroscopy may improve sensitivity for detecting marrow involvement. Even with these techniques, however, 10% of patients with acute myeloid leukemia, 41% of patients with chronic lymphocytic leukemia, and unknown percentages of patients with other leukemias have normal MR quantitative marrow analysis (Bongers et al; 1992).

Changes in T2 relaxation times of leukemic marrow are more variable. Although there may be some prolongation of T2 values, measured values show no statistically significant difference from those of age-matched control subjects. Of the various types of leukemia, acute myelogenous leukemia (in adults) and acute lymphocytic leukemia (pretreatment or in relapse in children and adults) demonstrate the most profound marrow changes by MRI (Volger III and Murphy, 2006).

MRI of femoral marrow in patients with acute leukemia fail to identify significant responder or relapse rates at the time of diagnosis. After therapy, however, femoral MR marrow patterns revert to normal
fatty marrow in patients who achieve remission and remain abnormal in those who do not achieve remission. Therefore, patients with abnormal femoral marrow by MRI after therapy should be followed closely even despite a normal frequency of marrow blasts on bone marrow biopsy (Takagi et al; 1995).

In chronic lymphocytic leukemia, patients who demonstrate prolonged T1 values on quantitative MR studies at the time of diagnosis have a poorer prognosis than those with normal range T1 values at presentation (Lecouvet et al; 1997). Similarly, patients with chronic lymphocytic leukemia who display abnormal quantitative MR findings or abnormal marrow distribution patterns have significantly higher marrow and blood lymphocytosis (two criteria used to diagnose the disorder) (Lecouvet et al; 1998).

Leukemic marrow often demonstrates regressive patterns by MRI after chemotherapy or radiation therapy for ablation of the leukemia. Acutely the MR changes are consistent with edema and congestion of the marrow. After the acute alterations have resolved, MR findings reflect normocellular or hypocellular marrow with corresponding shortened T1 values and comparable increased signal intensity on T1-weighted images. After this, regeneration of normal marrow can be seen. Quantitative MRI is a potential tool to monitor marrow changes in patients with leukemia under management (Volger III and Murphy, 2006).

Active leukemia is associated with diffuse infiltration of the bone marrow; in this process, normal hematopoietic elements and fat are replaced by leukemic cells. On T1 weighted MR images of the spine, this replacement is readily identified as diffusely diminished signal intensity of the vertebral body bone marrow. The marrow should gradually revert to normal if remission is achieved (Moore et al; 1986).
In patients successfully treated with bone marrow transplantation, the bone marrow appearance on MR images undergoes a predictable sequence of changes, reflecting the regenerative process. Stevens et al. 1990 reported that in 15 patients who had bone marrow transplantation, T1-weighted images obtained within 40-90 days after transplantation showed a band pattern of alternating zones of high signal intensity centrally and intermediate signal intensity peripherally. Direct cytologic examination of a vertebral body from one of those patients revealed that the zone of central hyperintensity corresponded to fat, and the peripheral zone of intermediate signal intensity represented reconstituting hematopoietic elements. If this band pattern does not develop or if the marrow signal remains diffusely hypointense on T1-weighted images, one should suspect failure of engraftment or possibly leukemic relapse. After the band pattern has been seen, the marrow appearance may revert to normal in the absence of leukemic relapse. Knowledge of the expected marrow appearance on MR images before and after bone marrow transplantation allows recognition of relapse and can help in understanding the process by which the bone marrow recovers following transplantation (Ginsberg and Leeds, 1995).

In both children and adults, leukemic marrow involvement is homogeneous, diffuse, and symmetric. Focal infiltration is more commonly seen in myelogenous leukaemia (Bredella and Stoller, 2007).

Bredella and Stoller, 2007, stated that the following findings are typical for leukemia:

- On T1-weighted images, leukemic hypercellularity is seen as low-signal-intensity replacement of higher-signal-intensity marrow fat.
- Due to the greater proportion of hematopoietic marrow in children, there is an overlap in the appearance of normal low-signal-intensity
cellular hematopoietic marrow and low- to intermediate-intensity hypercellular leukemic marrow.

- Quantitative measurements of T1 relaxation times have shown prolongation in patients with leukemia and leukemia in relapse. These assessments, however, are not specific for the diagnosis of leukemia. Prolongation of the T1 relaxation time is also seen in metastatic rhabdomyosarcoma or neuroblastoma. Normal bone marrow has a T1 relaxation time of 350 to 650 msec. At initial diagnosis of leukemia or in leukemia in relapse, T1 relaxation times of 750 msec have been identified. Further studies are needed to confirm the clinical significance of differences in T1 values among initial diagnosis, remission, and relapse.

- Conventional T2-weighted images may show increases in signal intensity in acute leukemia. Unlike the situation with metastatic disease, however, T2-weighted images may not be sensitive to leukemic hypercellularity.

- Quantitative measurement of T2 relaxation times in leukemia has not shown any significant difference from control marrow.

- Chemical-shift imaging has also been used to identify pathologic marrow. Relative changes in the fat fraction show the greatest potential for understanding changes in bone marrow signal intensity and changes occurring with relapse. Chemical-shift imaging may be more useful in adult patients because of the greater difference in the fat and water fraction of bone marrow.

- STIR techniques offer superior contrast for demonstrating increased signal intensity in leukemic marrow, exceeding that displayed by normal hematopoietic cells. Nulling of fat signal
intensity facilitates the detection of both focal and diffuse leukemic infiltrates.

Most chronic leukemias tend not to involve yellow marrow areas and in adults are characterized by a moderate to marked decrease in red marrow signal on T1-weighted images. Since red to yellow marrow conversion is complete in adults, leukemic involvement is more likely to be identified in the axial skeleton, pelvis, and proximal femurs. In children, leukemic involvement is more likely to be identified in the more peripheral sites of red marrow stores, such as the metaphysis, with diaphyseal or epiphyseal extension. Marrow cellularity can also be noninvasively assessed with MR imaging (Bredella and Stoller, 2007).

Bredella and Stoller, 2007 stated that the following MR findings are characteristic for chronic leukemia:

- In the acute phase of chronic leukemia, particularly in chronic myelogenous leukemia patients in blast crisis, there is almost complete replacement of both red and yellow marrow areas. The decreased signal on T1-weighted sequences represents replacement of marrow fat by tumor cells, which have a significantly longer T1 relaxation time. On STIR images, tumor cells appear as areas of white on a black or gray background.

- In primary myelofibrosis, T1-weighted images show patchy marrow involvement with low signal intensity on T1- and T2-weighted images. With STIR techniques, the imaging characteristics of areas of involvement are identical to those of normal hematopoietic marrow (i.e., intermediate to mild increased signal intensity).
Post-Chemotherapy Appearance of Marrow in Leukemia:

Patients with acute leukemia or chronic myelogenous leukemia in blast crisis are treated aggressively with myelotoxic drugs. This treatment results in cellular depletion (i.e., hypoplasia) of the marrow, accompanied by edema and fibrin deposition. Total depletion of the marrow may occur in a month or less, depending on the schedule of chemotherapy treatments and the sensitivity of the leukemic cells. As leukemic depletion progresses, fat cells (i.e., yellow marrow) regenerate. Normally, this phase of hypoplasia is followed by regeneration of hematopoietic elements (i.e., red marrow). Occasionally, however, extensive post-chemotherapy fibrosis develops. The fibrosis can be focal or widespread and may be accompanied by bone formation (Islam et al, 1980).

Chemotherapy produces a spectrum of MR changes in normal and leukemia marrow, including metastatic disease. These changes include:

- Marrow hypoplasia, characterized by the appearance of fatty marrow, demonstrates high signal intensity on T1-weighted images and intermediate signal intensity on T2-weighted images.
- With chemical-shift imaging, it is possible to demonstrate sequential increases in bone marrow fat fractions in patients in clinical remission during chemotherapy treatment for acute leukemia.
- Marrow fibrosis demonstrates low signal intensity on T1- and T2-weighted images.
- Reconversion of normal fatty marrow to hematopoietic marrow is seen as areas of decreased signal intensity on T1-weighted images and intermediate to mildly increased signal intensity on STIR images. When reconversion takes place adjacent to an area of signal intensity from fat in treated marrow, there is a reversal of the initial imaging signal intensity characteristics from pretreatment
bone marrow to post-chemotherapy marrow. Immediately after chemotherapy, marrow edema may falsely exaggerate the extent of disease progression. Follow-up examination can be performed to document a more accurate baseline \textit{(Bredella and Stoller, 2007)}.

In acute myeloid leukemia, MR imaging can demonstrate changes in bulk T1 during treatment that correlate with changes in bone marrow cellularity. However, these findings do not predict a favorable response to treatment \textit{(Bredella and Stoller, 2007)}.

\textbf{Myeloproliferative Disorders:}

Other myeloproliferative disorders (myelofibrosis, polycythemia vera, chronic myelogenous leukemia, and myelodysplastic syndromes) result from uncontrolled stem cell proliferation \textit{(Robbins et al; 1984)}. These disorders have not been extensively studied to date. In the setting of chronic myelogenous leukemia, MRI usually reveals a uniform pattern of marrow involvement. This uniform marrow pattern is observed to occupy the entire femur in chronic myelogenous leukemia patients with splenomegaly (adverse prognostic indicator), whereas only the proximal half of the femora tends to be involved in patients without splenomegaly \textit{(Takagi et al; 1995)}. After therapy, persistent abnormal femoral marrow patterns may indicate insufficient treatment despite normalization of white blood cell counts \textit{(Takagi and tanaka; 1996)}.

In myelofibrosis, marrow space is replaced to a variable degree by fibrosis. Fibrosis, along with hypercellularity, results in a lowering of marrow signal intensity on T1-weighted images. Because of the nature of replacement tissue (fibrous), marrow signal intensity is likewise diminished on T2-weighted images. In more advanced cases, where a larger amount of fibrous tissue is present, marrow signal intensity may be
substantially lower than that of muscle on long TR/TE spin-echo images
(*Lanir et al; 1986*)

In patients with polycythemia vera, the bone marrow of the axial skeleton is diffusely and homogeneously hypointense on T1-weighted MR images and it is indistinguishable from the diffuse marrow abnormality observed in patients with leukemia or myeloma. Foci of hypercellular marrow may appear in the peripheral skeleton as well. (*Moulopoulos and Dimopoulos, 1997*). *Kaplan et al; 1992* found that patients with polycythemia vera and nonfatty hypercellular marrow on MR images of the femoral epiphyses and greater trochanters had higher levels of serum lactate dehydrogenase and lower levels of serum cholesterol compared with patients with the same disease but with a normal fatty appearance of the proximal femurs.

Polycythemia vera causes marrow reconversion with expected signal patterns on T1- and T2-weighted images. The reconverted marrow displays signal intensity lower than that of fat and higher than that of muscle on both opposed and nonopposed short TR/TE sequences. The marrow appearance on long TR/TE images is much more variable. Reports describe decreased, normal, or increased signal intensity of involved marrow on T2-weighted sequences (*Lanir et al; 1986 and Jesen et al; 1988*). Factors believed to affect the variable T2 appearance include the fraction of cellular marrow, the amount of fibrosis, and the presence of hemosiderin from multiple transfusions. If present, fibrosis and siderosis would also be expected to lower T1 signal. The presence of nonfatty marrow in the femoral capital epiphysis and greater trochanter in patients with either myelofibrosis or polycythemia vera correlates with accepted clinical indicators of disease severity (high serum lactate dehydrogenase and low serum cholesterol) (*Kaplan et al; 1992*). Similarly, appendicular involvement patients with polycythemia vera
correlates with spleen size (an indicator of disease severity in these patients). As in leukemia, MR evaluation of the femora appears to offer advantages over studying the spine in patients with myelodysplastic syndromes. Femoral MRI may prove useful in distinguishing hypoplastic myelodysplastic syndrome from aplastic anemia and in monitoring myelodysplastic patients for therapeutic response or evolution to leukemia (Takagi and tanaka, 1996).

**Ewing’s Sarcoma:**

MR imaging of Ewing sarcoma is an effective method of depicting the extent of the lesion and showing intramedullary tumor, cortical disruption, and adjacent soft tissue involvement (Lemmi et al., 1990).

Ewing sarcoma demonstrates low signal intensity on T1-weighted sequences and high signal intensity on T2, fat-suppressed T2-weighted fast spin-echo, and STIR sequences. Marrow involvement and peritumoral edema are clearly delineated on fat-suppressed T2-weighted fast spin-echo images. There is usually a substantial soft-tissue component associated with Ewing sarcoma, which is well evaluated with MR imaging. Since MR imaging provides excellent delineation of soft tissues, the extent of muscular and neurovascular involvement in extraosseous Ewing sarcoma can be accurately assessed. In addition, Ewing sarcoma originating in bone marrow can be identified in the early stages, before cortical erosion and periostitis have developed. MR imaging has been used after chemotherapy to more accurately define tumor margins and assess the interval decrease in adjacent peritumoral edema (Bredella et al., 2007).

Lemmi et al., 1990 investigated changes in MR signal intensity before and after chemotherapy on serial imaging studies. They found that, On T1-weighted images, the normally bright fatty marrow cavity
was replaced by neoplastic tissue of approximately the same intensity as normal muscle. During chemotherapy, the soft-tissue component decreased markedly in size, or disappeared completely. The residual soft-tissue masses were apparent as dark lesions adjacent to or encircling the bony cortex and limited by an outer rim of dark signal consistent with bone. No change in T1-weighted signal intensity was apparent in either the responsive or nonresponsive lesions. On the initial T2-weighted images, both the bone-marrow and soft-tissue components had an intensity equal to or greater than that of fat but less than that of water. The bone marrow signal of all drug-responsive lesions increased in intensity during chemotherapy.

MR imaging demonstrates a soft tissue mass in approximately 80% to 90% of patients. This is seen best on T2-weighted or contrast-enhanced T1-weighted axial images. Similar to imaging of osteosarcoma, the T1-weighted longitudinal images define the intramedullary extent of tumor. Dynamic enhanced MR imaging examination early in treatment has a potential role for determining outcome and may be used in the decision to intensify treatment. With treatment, the soft tissue mass decreases in size and the intraosseous portion becomes necrotic with a higher signal on T2 weighting. MR imaging is more accurate than standard radiography, CT, or bone scintigraphy in the diagnosis of recurrent ES. CT is no longer used in the assessment of the primary lesion. Chest CT, however, is indicated to detect pulmonary metastases (Miller and Hoffer, 2001).