Primary neoplasms of the skeleton are rare, but metastatic involvement is, unfortunately, a common occurrence. This is particularly true for certain primary tumors. Skeletal metastases are clinically significant because of associated symptoms, complications such as pathological fracture and their profound significance for staging, treatment and prognosis.

Detection of bone metastases is, thus, an important part of treatment planning. The frequency with which metastases are detected varies considerably with the type of primary tumor and with the methodology utilized for detection.

Four main modalities are utilized clinically: plain film radiography, CT scan, nuclear imaging and magnetic resonance imaging. In this discussion, we will review literature on the radiology of skeletal metastases with respect to lesion detection, assessment of response to treatment and possible therapeutic implications. The bulk of the discussion will focus on MRI and nuclear studies since most of the recent advances have been made in these areas.

**Key words:** Neoplasm metastasis - Bone neoplasms secondary - Tomography, emission computed - Magnetic resonance imaging - Radiography.

Skeletal metastases are unfortunately common. The frequency with which they are detected varies considerably with the type of tumor. It also varies with the methodology used for detection. For some types of tumor, such as breast cancer, skeletal metastases are readily detected by imaging studies and form an important aspect of the clinical disease management because of the symptoms they produce. For other conditions (such as chordoma), disseminated skeletal metastases are frequently detected at the time of autopsy, but are less apparent during life.

In general, the prognosis for patients presenting with bone metastasis is poor. Patients with fewer metastases or solitary lesions appear to have a better outlook than those with multiple metastatic deposits.

**Mechanisms**

Direct invasion of the skeleton may result from an adjacent primary tumor (Fig. 1). Perhaps the most prevalent example is invasion of the chest wall by a lung cancer. Lymphogenous spread to bone is uncommon and difficult to document. However, secondary invasion of bone from involved lymph nodes is not rare. The spine is the most commonly affected site. The left side of the vertebral bodies is more often involved because the left-sided nodes are closer to bone than the right. Direct skeletal invasion is usually accompanied by a detectable soft tissue mass, a feature that is unusual in metastases that arise by hematogenous spread.

Most tumor implants occur through the hematogenous route. The venous, rather than arterial route appears more important, especially Batson’s paravertebral plexus. Presumably, the absence of valves in
these veins permits retrograde distribution of tumor cells. Batson’s plexus communicates with the axial skeleton and the proximal long bones resulting in a predilection for these sites. The preference for axial involvement is also due to the greater vascularity of the red (hematogenous) marrow found in the axial skeleton as opposed to the yellow (fatty) marrow found in the appendicular bones.

**Clinical features**

Many of the patients complain of bone pain, which may be due to various mechanisms including release of chemical mediators, elevated intra-osseous pressure, and periosteal elevation. The probability that a skeletal metastasis will be painful may partly depend upon the nature of the primary. Metastases from lung and breast primaries are more likely to be symptomatic than are those from prostate cancer. Fractures and impending fractures are also an important source of pain, particularly in weight-bearing bones. Such fractures are more common in areas involved with lytic metastases rather than blastic ones. They are difficult to manage, and often fail to heal.

Symptoms of arthritis may result from tumor in bone adjacent to a joint, mechanical collapse of an articular surface due to lytic metastasis, or from synovial implants of tumor. Primary malignancies that have been reported to present in the latter fashion include lung, colon, breast, melanoma, and rhabdomyosarcoma. Synovial implantation is very rarely documented on imaging studies.

Arthritic symptoms may also be due to paraneoplastic effects such as carcinoma polyarthritis, a condition in which there is sudden onset of rheumatoid-like symptoms with an asymmetric distribution in a patient who is rheumatoid-factor negative. Hypertrophic (pulmonary) osteoarthropathy is another paraneoplastic syndrome that may result in joint and long bone symptoms without local involvement.

Secondary gout is a known complication in cancer patients, especially after treatment. Skeletal changes due to radiation, such as osteonecrosis and fracture may be difficult to distinguish from metastatic lesions on imaging studies, but are usually not symptomatic. Finally, symptoms may be due to the onset of carcinoma-related rheumatic conditions such as Sjögrens syndrome, lupus, and dermatomyositis. The most common malignancy associated with arthritic symptoms is leukemia.

**Detection - radiography**

Radiography is commonly used to evaluate symptomatic sites and to confirm findings on other imaging studies. It is not generally recommended as a screening method because of poor sensitivity. The radiographic survey remains valuable in staging of multiple myeloma due to the poor sensitivity of the radioisotope scan in this condition.
Sensitivity depends partly on location. For instance, metastases to dense cortical bone are easier to detect than those involving trabecular (medullary) bone. In the axial skeleton, medullary metastases may not be detectable until 50% of the trabecular bone has been destroyed.

Among the advantages of radiography is the fact that certain features may help to distinguish metastases from other conditions and aid in identification of the primary tumor. Radiography may be used to assess the risk of pathological fracture, which is said to be high if 50% of the cortex is destroyed by a lesion. This is a crude measure at best. Recent work using quantitative analysis of CT scans for this purpose has shown much greater promise.

**Detection - CT**

CT scanning has had a limited impact upon the clinical detection of skeletal metastases. Although more sensitive than conventional radiography for the detection of destructive bone lesions, CT is a cumbersome tool for screening the entire skeleton. Interestingly, CT can detect metastases within bone marrow before bone destruction has occurred (Fig. 2). Tumor within the marrow causes an increase in attenuation due to fat replacement. An attenuation difference of more than 20 HU between the right and left extremities is abnormal. Such findings are subtle, and easily overlooked by the radiologist. They are far less apparent than the marrow changes seen on MRI.

**Detection - nuclear methods**

Since the introduction of technetium-based scan agents, approximately 25 years ago, the radioisotope bone scan has been the standard method for detection of skeletal metastases. Isotope scanning is more sensitive than radiography for detection of most metastases. Tracer accumulates in the reactive new bone that is formed in response to the lesion. Thus, although most metastatic lesions are "hot", cold lesions due to complete absence of reactive bone may be encountered in particularly aggressive metastases (Fig. 3). In addition, the amount of accumulation is sensitive to the level of blood flow. Diffuse accumulation of tracer throughout the skeleton due to disseminated skeletal disease (super scan) may lead to the false impression of a normal scan (Fig. 4).

The bone scan suffers from a lack of specificity. Tracer accumulation may occur in any skeletal location with an elevated rate of bone turnover and, thus, may accompany trauma, infection or arthropathy. The probability that an abnormal scan represents metastatic tumor is directly related to the number of abnormal foci. In a patient with foci of increased uptake and a known primary tumor, the scan strongly suggests metastases. A small number (less than 4) of abnormalities is more likely to represent metastatic disease in some locations than others, with rib lesions being particularly low-yield. Only 50% of solitary foci represent metastases, even among patients with cancer.

This lack of specificity is well known and has lead to recommendations that positive scans be accompanied by radiographic correlation. However, given the greater sensitivity of the bone scan, a positive radiograph may confirm a finding, but a negative radiograph does not exclude a metastasis.

Recent advances in isotope scanning methods, particularly single photon emission computer tomography (SPECT), have improved the detection of metastases. SPECT imaging has increased both the sensitivity and specificity of bone scanning. The tomographic presentation of SPECT images helps to identify foci of abnormal uptake especially in the thicker body parts such as the spine and pelvis. In addition, improved spatial localization helps to distinguish between met-
Astatic foci and other abnormalities causing increased uptake, such as spondylosis. Increased uptake that involves the posterior vertebral body is more likely to be due to metastasis.

A baseline radio-isotope bone scan is no longer recommended in stage 1 or 2 breast cancer because of low yield. Several recent studies have suggested that the diagnostic yield of bone scan in patients with small and well-differentiated prostate carcinomas and PSA values <20 is too low to warrant routine use. If scanning is withheld from such individuals the national savings would be $38 million/year. However, recent data indicates that for patients who have received androgen depletion therapy, the PSA may be unreliable in excluding metastases.

At present, the conventional bone scan has no role in the detection of metastases from renal cell carcinoma and head and neck cancer. For non-small cell lung cancer, the bone scan is still recommended at the time of diagnosis to aid in selection of patients for surgery, although FDG-PET is also promising.

There have been conflicting reports as to the efficacy of PET scanning and, as of yet, a consensus has not been reached. One study of 44 patients with known metastatic disease from lung, prostate and thyroid primaries showed FDG-PET to be more sensitive and specific than conventional bone scan. Schirmeister et al. studied 34 patients with breast cancer and concluded that FDG PET allowed for earlier detection of small marrow metastases than conventional bone scan and lead to clinically significant changes in management of four patients (Fig. 5).

Other results have not been as encouraging. A recent publication based on imaging of 98 bone lesions in 24 patients reported better specificity, but lower sensitivity for FDG-PET as compared to conventional bone scan. Another study similarly concluded that FDG-PET can detect prostate metastases to bone with moderate sensitivity (65%), but high specificity.
(98%), and may have some value in lesion detection. Yeh et al. reported dismal results in a small series of 13 patients with multiple bone metastases from prostate cancer in which FDG-PET only detected 18% of the lesions apparent by bone scan. The authors concluded that prostate metastases must have means other than glycolysis for metabolism and energy. With regards to breast metastases, one group reported that PET demonstrated superiority to bone scan with osteolytic metastases, but failed to consistently detect osteoblastic metastases. These observations suggest a possible role for PET similar to plain film radiography, as confirmation of positive results from conventional technetium scans, rather than a means of initial detection.

FDG appears not to be taken up by Paget disease, and, therefore, PET imaging may be useful to separate Paget’s disease and other benign conditions from metastases and/or sarcomatous degeneration. However, despite undeniable utility in certain circumstances, presently there is no established role for PET imaging in the clinical evaluation of bone metastases.

Marrow scanning has been reported to be more sensitive than the conventional bone scan in detection of metastases from prostate cancer. In one study comparing marrow imaging using 99mTc anti-NCA-95 monoclonal antibody with conventional MDP, the marrow imaging technique detected almost double the number of lesions seen on MDP scans. However, the number of patients identified as having metastases was the same: 13 in both instances. In another study of 23 patients with breast metastases, bone marrow immunoscintigraphy (anti-NCA 95 Mab 250/183) demonstrated better specificity (88 vs 75%) and positive predictive value (92 vs 85%) than conventional bone scan with no significant difference in sensitivity. Like PET, marrow scanning has not yet found a role in routine clinical practice.

For certain types of primary tumors, (especially lymphomas and soft tissue sarcomas) Gallium scanning may be a useful staging tool, detecting metastases that are not otherwise observed. It may also be helpful to follow the effect of treatment in these patients.

**Detection - MRI**

Magnetic resonance imaging (MRI) is highly sensitive to the presence of skeletal metastases within the bone marrow. Since bone marrow (including hematopoietic or “red” marrow) contains a high percentage of fat, T1-weighted magnetic resonance images generally reveal metastases as focal areas of low signal intensity. Lesions can be often be distinguished from focal deposits of red marrow on T1-weighted images because the latter are more focal and may have centrally located fat, giving the appearance of a “bull’s eye”. On fat-suppressed T1-weighted images, metastases demonstrate mixed to high signal intensity. On T2-weighted images, metastatic lesions usually are much brighter than normal marrow due to their high water-content (Fig. 6). Metastases often, but not always, have a rim of bright T2 signal around them (halo sign).

A variety of different MRI pulse sequences have been evaluated. In general, conventional spin-echo pulse
sequences provide the best signal-to-noise ratios and anatomical detail. However, because of the need for rapid evaluation of large regions, fast spin echo and inversion recovery image sequences have been tested and found to be acceptable. Castillo et al. reported that diffusion weighted imaging had no advantage over non-contrast enhanced T1 weighted imaging in detection and characterization of vertebral metastases, but was somewhat superior to T2 weighted imaging. It has become clear that magnetic resonance imaging can detect metastases that are not apparent on radioisotope bone scans. MRI is particularly well suited to detect spinal metastases, and most authorities agree that it is superior to planar scintigraphy for this purpose. This may be partly due to the difficulty of recognizing subtle radionuclide abnormalities, since retrospective review of the isotope scans may reveal many abnormalities that were initially missed. One study of breast cancer patients concluded that MRI was specifically superior to bone scan in detection of

![Fig. 5.—The utility of PET in the detection of metastatic disease was demonstrated in this patient with past history of Ewing’s sarcoma of the sacrum. A) A bone scan revealed foci of uptake in the lower right ribs which corresponded to a site of prior surgery, but no other suspicious sites. B) A subsequent PET scan revealed a focus of increased FDG uptake in the proximal right humerus suspicious for metastasis. C) Plain films of the area revealed no obvious abnormality. D) A T1 fat saturated coronal image of the right shoulder demonstrated an obvious focus of metastatic disease demonstrating diffuse enhancement.](image-url)
aggressive spinal metastases that demonstrated estrogen receptor negativity and increased biologic activity.\textsuperscript{33} Most studies that have compared MRI to bone scanning have used planar bone scans, not SPECT. Planar scintigraphy detects about 1/3-2/3 of the lesions seen by MRI. Multiple investigators have demonstrated the superiority of SPECT to planar imaging with regards to detection of vertebral metastases.\textsuperscript{34-36} Some authors believe that SPECT makes nuclear scanning comparable to MRI, with MRI better for vertebral body lesions and SPECT better for the posterior elements.\textsuperscript{37}

Advantages of the isotope scan include a large field of view, inexpensive radiopharmaceutical, low morbidity, and the ability to provide some functional and vascular information. MRI may be a simpler and less expensive method to evaluate the axial skeleton, but it has been considered less well-suited for screening the long bones. Because of this, some investigators have recommended that the role of MRI be restricted to clarifying an equivocal bone scan.\textsuperscript{38} However, one group took the position that lesions missed in the extremities were not significant. In their analysis of 200 patients with breast and prostate carcinoma, 3 of 4 peripherally located skeletal lesions that were missed by MRI were detected by plain film radiography because they were painful.\textsuperscript{39}

Identification of appendicular lesions by MRI has been facilitated by development of faster pulse sequences. Several recent papers have reported that in comparison to conventional bone scan, whole body MRI utilizing whole body fast short tau inversion recovery (STIR) sequences has significantly better sensitivity and specificity.\textsuperscript{40-43} One of these papers noted that detectability of rib lesions was suboptimal utilizing MRI.\textsuperscript{40} Walker et al. further suggest that whole body MRI for patients with breast cancer may prove to be an effective means of detecting skeletal, brain and liver metastases with one study.\textsuperscript{44}

There are a number of specific situations in which isotope scanning may be preferred to MRI. They include patients with contraindications to MRI such as claustrophobia and pacemakers, and patients with thyroid cancer in which scanning may be done with iodine. MRI is preferred when the differential diagnosis includes marrow diseases such as lymphoma, leukemia, myeloma and Waldenstrom macroglobulinemia.\textsuperscript{45-47}

The factors that influence the choice of imaging modalities continue to evolve. Progress in MRI has been particularly rapid, and it appears probable that its role in screening and staging in reference to skeletal metastases will continue to grow and that it may ultimately replace the isotope scan. Until that time, isotope scanning, especially with SPECT imaging, will continue to have an important role.

**Identification of the primary tumor**

Unfortunately, patients may first come to medical attention as the result of skeletal metastasis from an...
unknown primary tumor. For such individuals, imaging studies may be used to help identify the primary lesion. Common tumors with a high rate of bone metastasis include: breast 72%, prostate 84%, thyroid 50%, lung 31%, kidney 37%, pancreas 33%. Together, these account for more than 80% of primary tumors in patients presenting with metastases.48-50

Previous studies have reported limited success in identifying the primary tumor when a patient presents with skeletal metastasis of unknown origin. In general, the primary tumor has been identified in less than 50%, even when patients were followed to autopsy. In one of the most positive reports, the relative value of the history and physical examination, CBC, erythrocyte sedimentation rate, blood chemistries, alkaline phosphatase, plain films of the lesion, radioisotope bone scan and computed tomography of the chest, abdomen, and pelvis were compared. The primary tumor was identified in 34/40 (85%). Interestingly, the laboratory values were unhelpful. History and physical examination revealed the primary in 4, chest X-ray identified 17, CT of chest added another 6, and CT of abdomen/pelvis added another 5. If used alone, CT would have diagnosed 75% of all primaries on the initial evaluation. All other modalities, including follow-up CT only added an additional 10%.51

CT has an important role in providing imaging guidance for tissue sampling. Biopsy of the skeletal lesion, followed by examination of the tissue using sophisticated histologic techniques to limit the imaging search may be an equally valid approach to this difficult problem.48 One study, however, concluded that CT scanning may be used to identify the primary tumor.49 CT scanning was more sensitive in detecting the primary than plain film radiographs, mammograms, and bone scans.50

Radiographic features of the skeletal metastases may help direct the search for a primary lesion. Some primary tumors tend to result in metastases that are purely lytic in nature, such as lung, renal and thyroid cancer, others to be associated with variable degrees of sclerosis, especially prostate, breast, carcinoid and tumors of endocrine glands (Fig. 7).

Evaluation of treatment

The prognosis for patients presenting with bone metastases is poor. In one series, only 4/578 patients were free of disease 10 years after diagnosis of bone disease. Mean survival for patients with all primaries was 5 months after diagnosis.49 In general, patients with solitary lesions or a small number of metastases have a better outlook than those with multiple metastatic deposits.

Skeletal metastases may respond to the chemotherapy or hormone therapy used for the primary tumor. They may also respond to radiation, or agents designed to block bone resorption such as the new class of bisphosphonate drugs.53

Response of the skeletal lesions may result in reactive bone formation on conventional radiographs 54,55 (Fig. 8).

Sclerosis tends to progress from the periphery of the lesion toward its center. Progressive sclerosis may make subtle areas of bone involvement more visible, contributing to the false impression of disease progression. In one study of the effects of treatment, careful retrospective analysis of bone scans revealed subtle foci of increased uptake in many areas which showed progressive sclerosis, indicating that the lesions had been present prior to treatment.56

Isotope uptake usually decreases following treatment of a metastasis. Occasionally, increased uptake is seen, particularly in the early phases of therapy. This is known as the “flare phenomenon” (Fig. 9). Because of this, it has been suggested that an increasing number of lesions is a more reliable marker of disease progression than increasing intensity of uptake.

Areas of bone necrosis as a result of chemotherapy may mimic metastases, further confusing interpretation of post-treatment scans.57 Bone marrow scans using 99mTc antigranulocyte monoclonal antibody have shown promise as an alternative method of assessing treatment response.50

At least one author has suggested radiopharmaceuticals may be used to improve the timing of treatment with chemotherapeutic bone seeking agents. In that study, many patients with prostate cancer receiving androgen ablation therapy were found to demonstrate a peak in uptake of 99mTc-MDP about 3 weeks after institution of hormone treatment.58

Quantitative methods to evaluate the response to treatment have been elusive. In one study, CT density was used to evaluate response. Immediately after successful radiotherapy of vertebral metastases as judged by relief of pain, there was a decrease in density by 25% within the lesions, followed by an increase of 61% 3 months later. The bone surrounding the lesions
increased consistently from beginning to end.59 Other studies utilizing dual-energy X-ray absorptiometry (DXA) and quantitative bone scintigraphy to monitor disease progression and response to treatment have yielded equivocal results and further study in this area is necessary.60-62 MRI has shown some promise as a means of assessing treatment response. One group had good results.
using changes in the volume of the bone and soft tissue components of lesions on T1 weighted images as criteria in patients with breast cancer metastases. In four of the patients, MRI revealed a response when blood markers were equivocal and bone scan results suggested disease progression. Another study revealed similarly encouraging results in utilizing MRI in prediction of disease progression or stability in patients with breast cancer metastatic to the spine.

Several different MRI methods have been devised to follow the progress of therapy of the primary tumor. Of these, the most promising is the rate of uptake of gadolinium (so-called dynamic scanning). By this method, it appears to be possible to distinguish viable tumor from necrotic tissue and treatment effects. Similar methods have been applied to the evaluation of metastases. These methods, while showing promise in the investigational context, are not yet ready for routine clinical implementation.

**Image guided percutaneous biopsy and other interventions**

Progress in imaging technology, and especially the increased use of CT scanning for guidance, has greatly increased the safety and applicability of needle biopsy for skeletal metastases. Prior to the era of CT-guided procedures, needle biopsy was considered dangerous for spinal lesions above the lumbar spine. It is currently rare to encounter a lesion for which needle biopsy is not feasible.

Accuracy rates vary depending upon the nature of the lesions being biopsied. In general, however, biopsies of metastatic lesions have higher levels of accuracy than infections and primary tumors.

A particularly interesting evaluation of image-guided biopsy accuracy introduced the concept of effective accuracy, defined as the ability of the procedure to replace open biopsy. In this report, the overall
accuracy was approximately the same for metastases, infection and primary lesions. Effective accuracy was best for metastases (77%), since clinicians tended to disbelieve negative biopsies for infection (72%), and pathologists asked for more tissue in primary lesions (59%). The authors noted that if a biopsy (or other test) has to be repeated, it is worse than worthless since it adds expense and discomfort without improving care.

The increased ease and safety of access to lesions in a variety of different anatomical locations has also opened up therapeutic possibilities, including ablative techniques for palliation, (and potentially cure). At present, most such work has been concentrated on soft tissue metastases, especially in the liver.

The skeletal implications of this work are just being realized. In one study, 25 terminally ill patients with painful lesions previously treated unsuccessfully by radiation and/or chemotherapy, a small amount of 95% alcohol was injected under CT guidance. Seventy-four per cent of cases experienced reduction in analgesic needs within 1-2 days after the procedure. Another interesting report used CT guidance to perform tumor ablation with radiofrequency energy. It is likely that the near future will bring rapid growth in the role played by radiologists in the management of patients with metastatic disease.

References


