he skeleton, after the lungs and liver, is the third most common site of metastatic disease, and metastatic disease is the most common malignancy of bone. Half of the nearly 1.4 million cases of newly diagnosed cancers each year involve tumors that frequently metastasize to bone (Table 1). Prostate, breast, lung, kidney, and thyroid cancers account for 80% of skeletal metastases. A predilection for the axial skeleton is seen, perhaps owing to the venous blood flow in Batson’s plexus. Overall, the most common sites of bony metastases are the spine, pelvis, ribs, skull, and proximal femur. When rare acral (ie, distal) metastases to the hands and feet occur, they most commonly originate from a lung primary.

As postcancer survival has increased with improvements in treatment, the numbers of patients developing metastatic disease during their lifetime has also increased. In careful postmortem studies of patients who succumbed to malignancy, rates of skeletal metastases approached 70%. This number increased to 85% when only breast, lung, kidney, thyroid, and prostate primary cancers were considered. This article reviews the presentation and evaluation of patients with metastatic bone disease and discusses the management of these patients.

**CLINICAL EVALUATION**

**Presentation**

The presentation of metastatic bone disease is variable, but pain is the most common complaint. The pain of metastatic disease is usually insidious in onset and is present in 75% of patients at presentation. Painless lesions usually are diagnosed during staging or routine follow-up (eg, technetium bone scan) in patients with a known history of carcinoma. Night pain and pain incompletely relieved by rest are not specific for metastasis alone, but they are typical symptoms. Weightbearing bones may become symptomatic early in the course of disease, whereas bones such as the flat bones of ribs or sternum may remain asymptomatic until late in the disease, often until pathologic fracture occurs.

Figures 1 and 2 show the algorithms used for evaluation of the patient with suspected metastatic bone disease. The use of a schema such as these will diagnose 85% of suspected metastatic malignancies and their primary malignancies.

**History**

The history in a patient with suspected malignancy should be more thorough than is often required for other orthopaedic conditions. Risk factors for carcinoma, such as tobacco abuse, alcohol abuse, chronic infections (especially viral), exposure to ionizing radiation, exposure to carcinogens, and family history of cancer, must be thoroughly explored and specifically questioned. Many patients will not know, for example, that chronic hepatitis is a strong risk factor for hepatocellular carcinoma, or that ulcerative colitis portends a markedly increased risk for colon cancer. Past medical history should be carefully discussed and reviewed. Patients may not recall the removal of a small mole on their back unless specifically asked.

A review of symptoms should go beyond simply a question regarding malaise or weight loss. Inquiries about cough, dyspnea, hematuria, flank pain, urinary hesitancy and/or painful urination, endocrine symptoms, and the noticing of any “lumps or bumps” are only some of the required queries in this patient population. If not specifically addressed, the patient with undiagnosed metastatic prostate cancer, for example, may make no connection between his frequent urination and his hip pain.

**Physical Examination**

The physical examination should be comprehensive. Examination of the musculoskeletal system in isolation is inadequate in this patient population if one wishes to diagnose a yet undetermined primary malignancy or...
Table 1. Incidence of Primary Cancers that Frequently Metastasize to Bone (United States, 2004)

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Estimated Cases Diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>230,110</td>
</tr>
<tr>
<td>Breast</td>
<td>217,440</td>
</tr>
<tr>
<td>Lung</td>
<td>173,770</td>
</tr>
<tr>
<td>Kidney</td>
<td>35,710</td>
</tr>
<tr>
<td>Thyroid</td>
<td>23,600</td>
</tr>
</tbody>
</table>


locate additional sites of metastatic disease. In addition to a focused examination in the symptomatic area, examination of the breasts, thyroid, prostate, and skin should be performed when appropriate. Lymphadenopathy should be sought by palpation of the major lymph node chains (axillary, supraclavicular, and inguinal). A stool guaiac study may be helpful if a gastrointestinal primary malignancy is suspected. Hyperreflexia (eg, Chovstek’s sign) may be a sign of hypercalcemia, a risk in patients with bone malignancy. Additionally, careful examination for deep vein thrombosis is prudent in this high-risk group.

LABORATORY STUDIES

A complete blood count, erythrocyte sedimentation rate, C-reactive protein level, blood chemistries, and liver function tests should be ordered as deemed appropriate to rule out other diagnoses such as infection, hyperparathyroidism, or metabolic bone disease. A urinalysis to search for occult blood should be performed, as occult hematuria may be the only early finding in renal or bladder carcinoma. Additionally, a urine and serum protein electrophoresis to rule out multiple myeloma, and a prostate-specific antigen test to rule out prostate carcinoma, may be wise in some patients.

Subtle findings of anemia, thrombocytopenia, leukopenia, or abnormal liver function tests should not be dismissed without further evaluation, as these may support systemic findings of metastatic disease. An ionized calcium level is helpful in the identification of hypercalcemia, as low albumin levels may make total calcium values difficult to interpret. One should also remember that many carcinomas can cause fever and elevated acute-phase proteins (eg, C-reactive protein) in the absence of infection. Therefore, these findings in isolation do not rule out metastatic disease, nor do they empirically confirm the diagnosis of infection.

Although tumor markers such as carcinoembryonic antigen, CA-125, and CA 19-9 are extremely helpful in monitoring the response of certain cancers to treatment, they are of little, if any, value in the initial work-up of metastatic disease with an unknown primary.

IMAGING STUDIES

Radiographs

Radiographs of the symptomatic area are the first step in the imaging evaluation of suspected bone metastases. In addition, radiographs are important for the interpretation of abnormal findings on the technetium bone scan. The clinician should correlate the technetium bone scan with the plain radiographs prior to confirming the diagnosis of metastatic bone disease with the patient. Up to 30% of benign enostoses (bone islands) and most enchondromas exhibit increased uptake on technetium scans. Technetium scans are very sensitive but nonspecific in distinguishing malignant and nonmalignant abnormalities. Radiographs are often diagnostic for enchondromas, bone islands, bone infarcts, and other incidental findings in the cancer patient. Up to 40% of metastatic lesions may be missed on radiographic survey, because 30% to 50% of mineral loss or a lesion size of greater than 1.5 cm is typically required for consistent detection.9 One’s ability to see less dramatic findings is certainly enhanced if a positive bone scan localizes an area of interest for scrutiny. One must carefully inspect all the cortices to detect subtle bone destruction.

The radiographic appearance of metastatic disease may be purely lytic, purely blastic (sclerotic), or mixed. Metastases from prostate, bladder, medulloblastoma, and bronchial carcinoid tumors are most likely to be blastic in nature (Figure 3). Purely lytic metastases are usually secondary to renal, pulmonary, thyroid, uterine, adrenal, melanoma, or gastrointestinal cancers (Figure 4). Mixed lesions are typically due to primary cancers of the breast, ovary, testicle, cervix, or lymphatic tissues.10,11 It is important to remember, however, that any cancer can appear in any pattern. Traditionally, primary sarcomas are associated with periosteal reactions (eg, Codman’s triangle, sunburst reactions), but one must avoid the temptation to definitively diagnose metastatic disease from a radiographic impression alone. Misdiagnosis of a primary mesenchymal sarcoma of bone as metastatic disease, with subsequent internal fixation rather than resection, can compromise limb-salvage options and even the life of the patient.

Technetium Bone Scan

Technetium Tc 99m methylene diphosphonate scanning is a very useful adjunct study in the work-up for metastatic bone disease in a patient with known or suspected cancer. Tumor osteolysis (directly caused by
osteoclastic resorption) causes a compensatory hyperemic and coupled osteoblastic response of varying degrees; this activity is responsible for the deposition of radioisotope tracer and, therefore, a positive finding on the test (Figure 5).

Tracer uptake on technetium bone scanning is not specific for metastatic bone disease. Monostotic lesions identified by technetium scanning in patients with known cancer will be proven to be metastases in only 50% of cases, underscoring the importance of a biopsy for confirmation, even in a patient with a known primary malignancy. Benign lesions such as enchondroma, infection, Paget's disease, stress fracture, and enostoses also may cause increased tracer uptake. Additionally, second primary cancers of mesenchymal origin (eg, chondrosarcoma) are rare but do occur. Multiple positive polyostotic findings in a patient with a known cancer are most likely to be metastatic disease, but a biopsy of a readily accessible site is still wise in the absence of visceral metastases.

A false-negative bone scan may occur despite the presence of single or multiple lesions from multiple myeloma (or solitary plasmacytoma), melanoma, Langerhans cell histiocytosis, lymphoma, leukemia, thyroid carcinoma, neuroblastoma, purely lytic lung carcinoma, or, rarely, breast cancer. Some authors argue against the use of routine bone scanning for staging of squamous cell cancer of the head and neck, bladder cancer, and melanoma because of the very low incidence of bony metastases in these cancers. The presence of bone pain, however, should prompt such an evaluation.

In the setting of diffuse metastatic disease, the
increased uptake may be so diffuse and marked that no single area appears intense; this can result in the bone scan appearing normal. This phenomenon, termed a "superscan," can be diagnosed by looking for "renal steal," which is the absence of the normal renal uptake pattern that results from the excretion of excess isotopes. This pattern may also be seen in patients with poor renal clearance, however, and should not alone lead to the diagnosis of diffuse metastatic disease. Bone scanning for metastatic thyroid carcinoma can be improved with the use of technetium-99m methoxyisobutyl isonitrile.13

**Computed Tomographic Scan**

A computed tomographic (CT) scan of the chest, abdomen, and pelvis can be studied to search for primary disease, as well as to look for lymphadenopathy or metastatic disease in the lungs or liver. A CT scan of the local site of metastasis is occasionally performed and may
provide excellent osseous detail. This may be useful in the evaluation of subtle cortical irregularities or mineralized lesions in the medullary cavity or soft tissues.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is often performed at the site of metastatic disease. MRI is often useful in cases in which the bone scan is negative but localized symptoms are present. In addition, MRI is more sensitive than technetium bone scanning in the detection of bone metastases because earlier marrow abnormalities may be identified\(^{14}\) (Figure 6). MRI is the gold standard for evaluation of soft tissue masses.

In the spine, MRI is valuable in assessing the extent of involvement as well as evaluating for spinal cord or nerve root compression. Additionally, MRI can occasionally be helpful in determining the extent of disease and marrow involvement in patients requiring radiotherapy postoperatively or for palliation.

**Positron Emission Tomography**

Positron emission tomography (PET) utilizing fluoro(deoxy)glucose is becoming more widely available. PET scans have the potential of both high sensitivity and high specificity. In some malignancies, such as thyroid cancer, the results of the PET scan may be positive while results of all other diagnostic modalities (ie, radiograph, bone scan, MRI, CT) are negative. As clinical trials of PET scanning in the orthopaedic setting continue, the use and understanding of this diagnostic modality is certain to increase.
BIOPSY

It is generally prudent to confirm the diagnosis of bone metastases with biopsy. A solitary bone lesion in a patient with cancer should not be assumed to be from the patient’s cancer. In addition, in cancer patients who develop bone lesions without the presence of visceral metastases, biopsy should be considered to confirm the diagnosis. A biopsy should be viewed as a confirmatory study of metastatic disease—in only a minority of patients can the primary site of the malignancy be diagnosed by biopsy alone. In polyostotic lesions, the most easily accessible lesion should be chosen for biopsy. If, however, there exists an area of impending fracture, this site may be biopsied at the time of surgical stabilization if frozen section confirmation of metastatic disease is available at the institution.

Biopsy may be performed via fine needle aspiration, CT-guided needle or core sampling, or via open techniques. Open techniques typically require operative time and often the risk of anesthesia. The choice of biopsy technique must be based on the lesion size and location, the surgeon’s experience, the experience of the

Figure 6. (A) Anterior-posterior radiograph of the hip of a patient with metastatic breast carcinoma. A poorly marginated lesion in the greater trochanter is visible, with thinning of the cortex. (B) Coronal T1-weighted magnetic resonance imaging scan of the pelvis. A low-signal lesion can be seen occupying the entire greater trochanter and extending down to the subtrochanteric level. On the opposite (left) hip, multiple round, low-density, low-signal lesions are visible in both the proximal femur and the acetabulum, consistent with metastatic bone disease. (C) A coronal inversion recovery sequence shows high-signal activity in the greater trochanter extending to the subtrochanteric level, masking the area of involvement seen on the T1-weighted image.
radiologist, and the preferences of the musculoskeletal pathologist who will be making the histologic diagnosis.

If a primary sarcoma is a possibility, the biopsy must be performed in a manner that will not complicate or compromise future oncologic resection or possible limb-salvage procedures. In most cases, if a primary sarcoma is suspected (eg, no primary cancer is found after work-up, or a patient with a distant history of cancer has a solitary lesion and no other evidence of active disease), the patient should be referred for biopsy to an orthopaedic oncologist who can perform the definitive procedure.

In cases of an isolated renal or thyroid metastasis, oncologic resection with wide margins may be indicated because of the possibility of cure in isolated metastatic lesions with these diagnoses. These patients should be considered for referral to an orthopaedic oncologist as well.

Histologic examination of bone biopsy specimens can differentiate metastatic disease from multiple myeloma, lymphoma, or primary sarcoma. Metastatic bone lesions show a consistent pattern of clusters of epithelial cells grouped in a glandular pattern in a fibrous stroma (Figure 7).

TREATMENT

There are 4 basic tenets in the orthopaedic treatment of metastatic disease to bone: pain control, prevention and treatment of fractures, maintenance of patient independence, and prevention of tumor progression.

Pain Control

Pain from bony metastases can be caused by tumor biology and the local effects of bone destruction or by the resultant structural insufficiency. Bone pain without structural insufficiency is often effectively treated with narcotic analgesics and radiation therapy, usually external-beam irradiation. Patients often benefit from hormonal therapy (eg, in metastatic prostate carcinoma), cytotoxic therapy, and/or bisphosphonate therapy. Bisphosphonates have been shown to improve pain and reconstitute bone stock. Some bisphosphonates may decrease tumor cell burden through induction of tumor apoptosis.16

Prevention and Treatment of Fractures

Prediction of fracture risk. Surgical stabilization to prevent pathologic fracture can immediately improve pain, mobility, and independence. Clinicians are often required to determine the appropriateness of surgical intervention in patients referred for "impending fracture." The criteria for impending fracture are in no way absolute, and the clinician must consider the patient’s surgical risk stratification, estimated life expectancy, and previous level of function when making decisions regarding the appropriateness of surgery as well as the implant type to be recommended. Many criteria exist in the literature for prediction of fracture risk,17–21 but none have been decisively supported in clinical trials. Important factors include the amount and pattern of bone destruction, the location of the lesion (or lesions), and the quality of associated pain.

The amount of bone destruction is the most important variable to be considered. The amount of involvement requires assessment of 2 orthogonal radiographs, through which 4 cortices are assessed and their involvement summed. Fidler20 has shown that fractures are highly unlikely (2.3% risk) when less than 50% of the cortical bone is involved, but very likely to occur (80% risk) if 75% of the cortical bone is involved. Eccentric lesions are more worrisome than similarly sized lesions that are located centrally. The pattern of bone destruction is also significant. Purely blastic lesions are least likely to fracture. Purely lytic lesions are the most likely to cause bone failure and the least likely to heal. Mixed lesions are of intermediate risk.22,23 Location of the lesion is also of paramount importance. Areas of high stress, such as the femoral neck and subtrochanteric regions, or the humeri in patients using walkers, are most likely to be exposed to forces in excess of the bone’s ultimate strength.

Weightbearing pain is another important predictor of fracture. When patients experience pain with every step that decreases with rest, structural insufficiency is likely present during normal physiologic loading. If, however, pain is present at night and at rest, then this pain may be due to tumor biology rather than structural osseous insufficiency.

Serial radiographs are often helpful in monitoring disease progression. Certainly, all patients treated conservatively for metastatic disease should have follow-up radiographs to evaluate progression of disease.

Surgical options. A complete discussion of surgical options for metastatic disease is beyond the scope of this review. Plates, intramedullary devices, and prosthetics all have their specific places in the orthopaedist’s armamentarium. Plates with methylmethacrylate augmentation are quite useful for metaphyseal and epiphyseal fixation but require an intact articular surface and sufficient nearby bone stock for fixation. At least 1 intact cortex is typically required to achieve rigid fixation and allow full weightbearing postoperatively if plate fixation is utilized. Reamed intramedullary nails have a
neutral axis almost identical to that of the bone in which they are placed. This load-sharing device, with a small-moment arm and low transmission of torque, confers excellent implant survival despite immediate full weightbearing. Large destructive lesions, intra- or peri-articular lesions, and lesions not permitting rigid fixation may require prosthetic replacement. Modular and custom complex prostheses are available.

One useful adjunctive procedure to be considered in the treatment of metastatic disease is preoperative tumor embolization. Most, if not all, metastatic lesions are hypervascular. Some lesions, especially renal metastases and myeloma, are notorious for the rich vascular network associated with them. This hypervascularity can be a source of markedly increased perioperative risk, as massive intraoperative blood loss can cause death, especially in patients with chronic illness and minimal physiologic reserve. Significant decreases in blood loss are seen with preoperative embolization.24 Embolization can be expected to be successful in up to 90% of cases.25,26 Metallic coils, polyvinyl alcohol beads, or gelled sponges may be used. With coils or polyvinyl alcohol, a 24- to 36-hour delay before surgery will not have a detrimental effect.24 Surgery should take place within 24 hours if gelatin is used to minimize loss of effectiveness via resorption of gelatin and recanalization of vessels. Embolization is especially helpful if reaming through a tumor is to be performed. Embolization may also be used as a method of pain control in patients who are not candidates for surgery.27–29

Prevention of Tumor Progression

In virtually all patients undergoing prophylactic fixation for metastatic disease, postoperative external-beam irradiation is warranted. Townsend et al30 found that 15% of patients treated with surgery alone required a second surgical procedure because of increasing pain or subsequent loss of fixation. In comparison, only 3% of patients who received postoperative radiation therapy needed additional surgical procedures.

Radiation therapy should be initiated after fixation and usually is begun 2 to 4 weeks postoperatively. The dose administered is 20 to 30 Gy divided into 5 to 10 fractions. The radiation field should include the original site of disease and the entire implant or fixation device, along with an adequate margin.31 In patients with life expectancies greater than 12 months (eg, those with solitary breast or renal metastases with no active primary disease) larger doses (eg, 45 Gy divided into 1.8-Gy fractions) may be warranted.

PROGNOSIS

Unfortunately, virtually all patients with bony metastatic disease eventually succumb to cancer. Median survival ranges from 6 to 48 months, but it is difficult to predict an individual patient’s prognosis. The median survival after the development of bony metastases is 48 months for thyroid carcinoma, 40 months for prostate cancer, 24 months for breast cancer, and 6 months for melanoma, kidney, and lung cancers.32 However, these are averages. For example, a patient with renal cell carcinoma, a 2-year disease-free interval, no visceral disease, and a nonaxial metastasis may live for many years. Discussion of the variety of positive and negative prognostic factors for each disease is beyond the scope of this review.

CONCLUSION

The management of metastatic bone disease is

(continued on page 39)
complex and requires a multidisciplinary approach. The evaluation must be thorough regardless of whether the patient has a previously diagnosed cancer. The treatment is geared toward controlling pain, preventing and treating fracture, maintaining the patient’s independence, and preventing progression of the tumor. Surgeons, radiation and medical oncologists, radiologists, physicists, therapists, nutritionists, and pain clinicians must collaborate to maximize the patient’s longevity and quality of life and to coordinate care in an expeditious and logical manner.

REFERENCES


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