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Optimal management of metastases to bone requires a multimodal approach.

Overview of Diagnosis and Management of Metastatic Disease to Bone

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Background: *Bone metastases occur frequently in patients with advanced cancer and are a serious complication of cancer. The decision to treat is often individualized, based on each patient's clinical presentation, life expectancy, and quality of life.*

Methods: *We reviewed the current literature pertaining to management of metastatic disease to bone, and the medical, radiotherapeutic, and surgical treatment options for management of bone metastasis are discussed.*

Results: *Current management of skeletal metastasis includes analgesia, systemic therapy, radiation therapy, and surgery. We propose treatment algorithms for management of vertebral and nonvertebral bone metastases and suggest individualized interventions based on clinical presentation.*

Conclusions: *Management of bone metastases is complex and requires a multidisciplinary approach. The goal of treatment is often palliative, and intervention and treatment regimens should be individualized based on the specific clinical presentation of each patient.*

Introduction

Bone is the third most common organ affected by metastasis, after the lungs and the liver. Approximately 400,000 patients in the United States develop skeletal metastases annually.[1] Breast and prostate cancers metastasize to bone more frequently, partly because of the prolonged clinical course and high incidence of these malignancies. An estimated 70% of patients with breast and prostate cancers develop bone metastases compared with 20% to 30% of patients with lung or gastrointestinal cancers.[2]

Skeletal-related events (SREs) due to bone metastases cause a variety of morbidities, including pain, pathological fracture, hypercalcemia, and spinal cord compression. Such events may cause significant debilitation and may have a negative impact on quality of life and functional independence. Current management of bone metastases is aimed primarily at reducing morbidity due to SREs so that quality of life and functional independence can be preserved or improved. Prevention of SREs and improvement in survival are the goals of current and future research.

To objectively assess and quantify quality of life in patients with bone metastases, several questionnaire-based tools have been developed. For example, the European Organisation for Research and Treatment of Cancer recently developed the Quality of Life Questionnaire (EORTC QLQ-BM22), a 22-item module designed

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to measure symptoms, functions, treatment side effects, psychosocial variables, and expectations of patients with bone metastases. Tools such as these can improve the ability to evaluate baseline measures and outcomes after a chosen therapeutic regimen for bone metastases and allow physicians to recommend certain interventions tailored to the needs of each individual patient.

This article summarizes the current management of bone metastasis and proposes clinical pathways for this common but complex and debilitating diagnosis. Subsequent articles in this issue thoroughly discuss each treatment modality and research directions for various interventions.

Clinical Presentation

Many metastatic bone lesions cause no or few symptoms and are diagnosed incidentally during an initial staging workup or at follow-up restaging evaluations. If symptoms are present, pain is often the main symptom for patients with skeletal metastasis. In fact, bone metastases are the most common cause of chronic pain in cancer patients. Pain varies, ranging from intermittent and indolent to sharp, severe, and radiating. It tends to be worse at night and may be partially improved with activity. Direct infiltration, fracture, or invasion to adjacent structures results in progressive and constant pain.[3]

When a pathological fracture is a presenting sign, it most often occurs with osteolytic lesions, with the majority of cases in patients with metastatic breast cancer.[4] Hypercalcemia occurs in about 10% of patients with bone metastases, is mediated by factors such as parathyroid hormone-related protein released by tumor cells and osteolysis,[5] and is predominantly seen in patients with breast cancer, multiple myeloma, and squamous cell lung cancer. Neurologic symptoms can be caused by vertebral metastases that can lead to spinal cord compression or spinal instability, which may result in a debilitating impact on quality of life and functional independence. Loss of ambulatory ability is a poor prognostic factor in patients with metastatic disease.[6-8]

Radiographic Diagnosis

Imaging studies are helpful in evaluating symptomatic sites, but none is currently recommended as a screening tool for all patients because of a low sensitivity for screening. A plain x-ray radiograph is often an initial diagnostic test for evaluation of bone pain to assess bone structure and mechanical alignment. However, osteolytic changes may not be detected on a plain radiograph until there is bone mineral loss of 25% to 50%.[9] Such an osteolytic abnormality places patients at high risk for pathological fracture.

Technetium-99 (^{99m}Tc) bone scintigraphy is a nuclear imaging study that is sensitive for identifying osseous metastases regardless of symptoms. It provides total skeletal examination, has a relative low cost, and thus is often the initial imaging modality for detection of bone metastases.[10] ^{99m}Tc shows an osteoblastic bone reaction by accumulating in reactive bones, where an elevated rate of bone turnover occurs. However, ^{99m}Tc bone scan cannot detect pure osteolytic metastases, and the poor specificity of this scan as well as its lack of anatomic detail often require that anatomic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) be obtained for further characterization.[9]

False-negative bone scans are also possible for highly aggressive and rapidly growing lytic tumors because of minimal reactive bone formation[11,12]; these tumors are better detected by metabolic scans such as fluorodeoxyglucose-positron emission tomography (FDG-PET) because they have a high glucose metabolism. Single-photon emission computed tomography (SPECT) improves the sensitivity and specificity of ^{99m}Tc bone scans for detection of small bone metastases,[13,14] but its use has largely been replaced by the wide availability of MRI, which provides a superior quality tomographic image.

CT and MRI can evaluate suspicious findings on ^{99m}Tc bone scans and can provide better spatial resolution and three-dimensional anatomic information about the skeleton as well as soft-tissue involvement. CT is recommended to evaluate structural integrity since CT is superior to MRI in revealing cortical integrity and the extent of structural destruction.[9] MRI is highly sensitive to detect small skeletal metastases not yet detectable on bone scans by revealing abnormal bone marrow; focal low-signal intensity on a T1-weighted image mix/high intensity on a fat-suppressed T1-weighted image and high intensity on a T2-weighted image are diagnostic of metastases.[15,16] MRI is particularly useful in detecting vertebral metastases and in determining disease extension around the spinal cord, aiding surgical and/or radiation therapy planning. A disadvantage of MRI is that it may be difficult to distinguish changes due to treatment, fracture, or tumor.[17]

Given the ability of FDG-PET to identify metabolically active skeletal metastases, which may or may not have detectable structural destruction, its use as an initial staging study and during follow-up evaluation is increasing for several malignancies such as lung, breast, and head and neck cancers. Early detection of malignant bone marrow infiltration can be demonstrated by increased glucose metabolism. Although FDG-PET is superior in detecting osteolytic metastases, it is less sensitive than ^{99m}Tc bone scans for detection of osteoblastic metastases.[18,19] Therefore, the sensitivity of FDG-PET may vary among different histologies. When compared with ^{99m}Tc bone scan, FDG-PET is more sensitive for myeloma, equivalently sensitive for breast and lung cancers, and less sensitive for prostate cancer. The aggressiveness of the tumor may also influence the sensitivity of detecting bone metastases using FDG-PET.[20]

Skeletal PET using F-18 sodium fluoride (NaF-18), a positron-emitting bone-seeking tracer, is another unique nuclear imaging modality. The available literature shows that NaF-18 PET is substantially more sensitive and specific than ^{99m}Tc bone scan and SPECT [21,22] for detection of metastases, especially for osteolytic lesions, but higher cost and greater radiation dose are among the disadvantages of NaF-18 PET.[23] Further studies focusing on cost-effectiveness may optimize the use of bone PET. All nuclear imaging modalities have limited spatial resolution, and therefore complementary CT is needed for localization of regions with abnormal glucose metabolism.

Therapeutic Options

The management goals of metastatic disease to bone are to (1) maximize pain control, (2) achieve functional preservation and restoration, (3) stabilize the skeleton, and (4) control the tumor locally. Asymptomatic bone metastasis with no risk of pathological fracture or spinal instability is often observed. The choice of treatment depends on several factors, including overall clinical condition, life expectancy, and quality of life. These factors play important roles in determining the choice of therapeutic intervention for bone metastases.

Current management of skeletal metastasis includes pain management/analgesia, systemic therapy (bone-modifying agents, chemotherapy, hormone therapy), radiation therapy (external-beam radiation therapy [EBRT], radiopharmaceuticals), and surgery. Optimal treatment of skeletal metastasis is complex, and a multidisciplinary approach is often needed; medical, surgical, and radiation oncologists working together with radiologists and pathologists develop multimodality treatment recommendations. Early detection and aggressive management of metastases can improve the quality of life and functional independence of patients.

Skeletal metastasis is complex and often the treatment recommendation is individualized to tailor each patient's specific clinical presentation and symptoms. Suggested algorithms and pathways for general management of vertebral and nonvertebral bone metastasis are depicted in the Figure.

Analgesia

Analgesic medication is the first-line therapy for pain management and is often administered with a stepwise approach. If pain is mild, initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen can be used. Nonopioid analgesics such as tramadol are recommended for mild to moderate pain. If pain is suboptimally controlled, opioids should be prescribed. For moderate to severe pain, analgesics should be administered on a fixed-dose schedule to provide constant pain relief. If breakthrough pain occurs, it can be effectively relieved with short-acting opioids such as oxycodone or hydromorphone; transmucosal fentanyl provides a rapid onset and is specifically indicated for cancer-related breakthrough pain.[24-27] Corticosteroids, neuroleptics, tricyclic antidepressants, and nerve blocks may be used as adjunct treatment to improve pain control.[28] A detailed discussion regarding the management of pain in metastatic bone disease including these specialized interventions is included elsewhere in this issue (Buga S, Sarria JE; pp 154-166).

For many patients, combination analgesic therapy is used to target different mechanisms while decreasing the side effects of each medication. However, few studies evaluating drug combinations for chronic cancer pain have been reported. In many situations, pain management should be considered to optimize combination analgesic therapy. It is important to design a personalized treatment schedule that achieves balance between adverse effects of the drugs and pain relief. Symptom monitoring and continuous evaluation are needed because modification of drug regimens may be necessary to optimize pain control and minimize drug-associated side effects.[29]

Systemic Therapy

Bisphosphonates bind preferentially to bone at the site of active bone resorption and inhibit bone resorption by blocking recruitment and activation of osteoclasts. Pamidronate and zoledronic acid are approved in the United States to treat cancer-related bone complications.

In several randomized clinical trials, intravenous bisphosphonate therapy was shown to delay the onset and lower the incidence of SREs in patients with bone metastases from solid tumors and multiple myeloma.[30-32] It can also be considered as an alternative therapy for pain relief in patients with widespread and poorly localized pain due to bone metastasis.[33,34] Approximately 50% to 75% of patients experienced mild to moderate pain improvement in 1 week, and the duration of pain control averaged approximately 12 weeks. In addition, in patients with bone metastasis who present with hypercalcemia, intravenous bisphosphonates with rehydration therapy is standard therapy.[35] The optimal duration of bisphosphonate therapy has yet to be determined, and therefore patients usually remain on this therapy indefinitely.

Denosumab, a human monoclonal antibody that binds and neutralizes receptor activator of nuclear factor κB ligand (RANKL), protects bone from degradation. Several recently published randomized clinical trials demonstrated that denosumab was superior to zoledronic acid in delaying the time to first SRE in patients with breast cancer and other solid tumors,[36-38] and these results led to the approval of denosumab for the prevention of SREs in patients with bone metastases from solid tumors by the US Food and Drug Administration in November 2010.

For certain malignancies that involve bone, such as myeloma and lymphoma, systemic chemotherapy

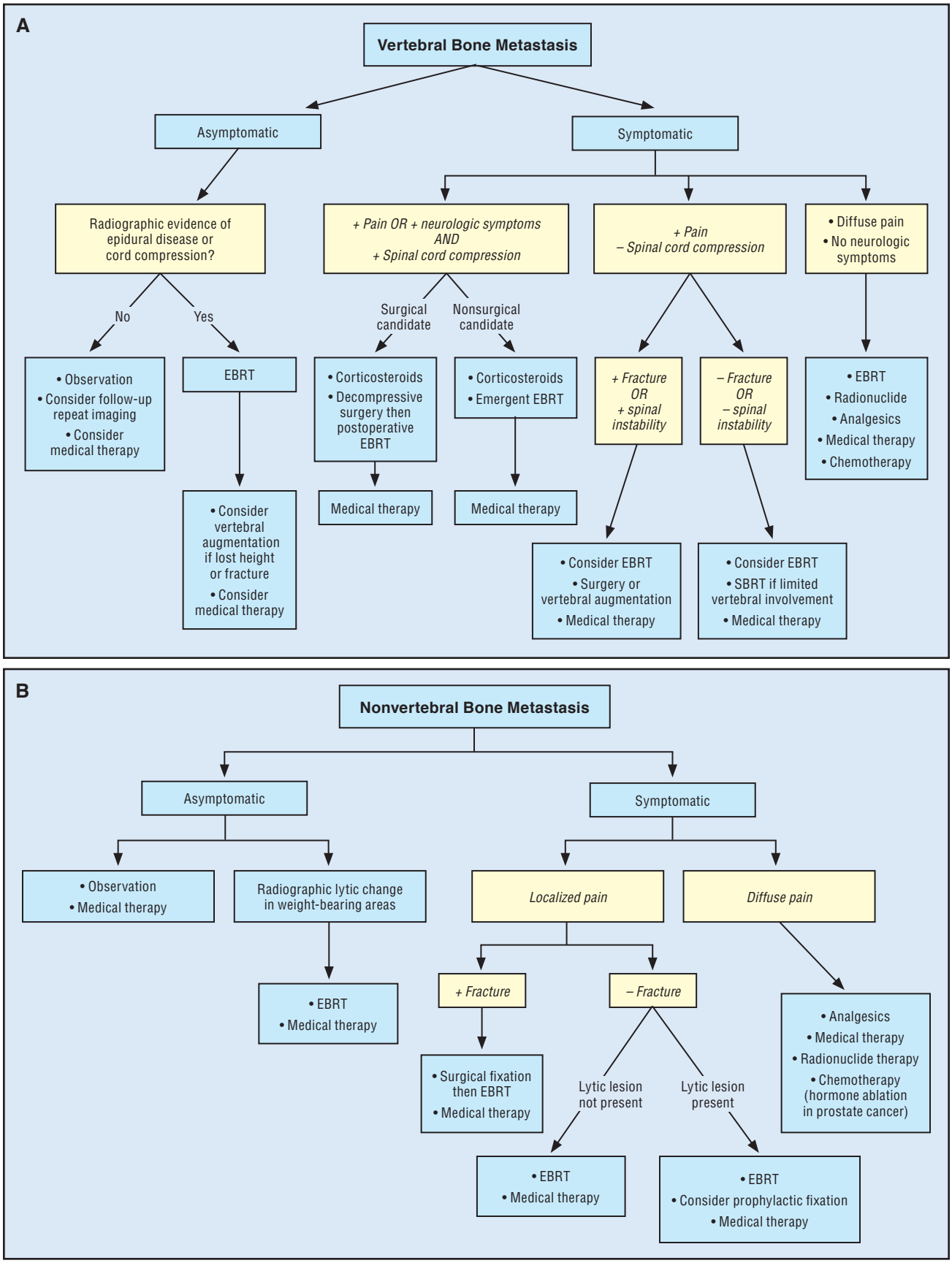

Figure. — Suggested algorithms for the management of (A) vertebral bone metastasis and (B) nonvertebral bone metastasis. Medical therapy includes bisphosphonates and a RANKL inhibitor. Pain management considered for all patients as appropriate includes analgesics (eg, NSAIDs, opioids, corticosteroids). EBRT = external-beam radiation therapy, SBRT = stereotactic body radiation therapy.

may provide an analgesic effect as well. In addition to radionuclide therapy, androgen deprivation therapy is another systemic treatment option for widespread painful bone metastasis from prostate cancer. Radionuclide therapy is described in detail in the following section.

Radiation Therapy

For palliation of painful bone metastasis, EBRT is the most common treatment, and it is a highly efficacious treatment option for patients with localized symptomatic skeletal metastasis.[39,40] Radiotherapy achieves pain relief by destroying tumor cells, thus reversing inflammation due to bone metastasis and promoting the ossification of lytic lesions.

Several fractionation schedules are used, with 30 Gy in 10 fractions being the most common in the United States.[39] The optimal dose and fractionation regimen for pain palliation of metastatic bone disease has been a subject of investigation. A number of clinical trials[41-50] demonstrated that short fractionation schedules were as effective as more protracted schedules.

A meta-analysis by Wu et al[51] included 3,260 patients from 8 randomized trials and compared single 8-Gy fraction with several multifractionation regimens. They found equivalent complete pain relief in about 33% of patients and a similar overall pain response rate of approximately 60% in both the 8-Gy regimen and the multifractionation regimens. Another meta-analysis of 11 trials by Sze et al[52] reported similar findings. Fewer treatment visits and patient convenience are advantages of single-fraction therapy. However, the need for retreatment may be higher for those who receive short-fractionation treatment. Hartsell et al[43] reported that the rate of re-treatment was 18% after single-fraction therapy vs 9% after fractionated therapy.[43]

A recent evidence-based guideline from the American Society of Radiation Oncology Task Force concluded that there is no difference in pain relief by spine vs nonspine metastasis. The Task Force and multiple prospective trials also found no evidence that single 8-Gy treatment provided inferior pain relief in patients with painful spinal metastases, nor did they demonstrate significant long-term side effects after single-fraction treatment.[53] Therefore, decisions regarding fractionation may be individualized. For patients whose life expectancy is less than 3 months, short-course palliative radiotherapy (such as 8 Gy in 1 fraction) can provide effective palliation while minimizing multiple treatment visits.

Stereotactic body radiation therapy (SBRT) is an emerging tool to treat select patients with vertebral metastases and may be particularly helpful in the reirradiation setting. This technology allows the delivery of a high ablative radiation dose by utilizing precisely targeted radiation to vertebral metastases while minimizing the dose to the spinal cord with a highly conformal technique and image-guidance treatment delivery. For sites that have been previously irradiated near the spinal cord, a significant concern about normal tissue toxicity of the spinal cord makes SBRT a valuable technology to retreat the same body site safely, with sufficient doses for palliation and/or local tumor control.

In recent years, clinical evidence has shown that this approach to delivering an ablative radiation dose using either a single-dose fraction or a limited number of dose fractions can lead to excellent pain control as well as local tumor control for a limited number of bone metastases to the vertebrae.[54-57] Prospective clinical trials, such as one led by the Radiation Therapy Oncology Group (RTOG), are currently comparing SBRT and a single 8-Gy fraction for painful vertebral metastasis. Results from these trials should provide clinical evidence for the utilization of this technology.

The cost-effectiveness of this new technology in palliation was recently studied by Haley et al.[58] In this matched-pair analysis, pain control at 1 month in patients treated with SBRT was similar to patients treated with conventional radiotherapy. The cost of various fractionated conventional radiotherapy treatments was 29% to 71% of the SBRT cost, but patients treated with conventional radiotherapy had more acute side effects and were more likely to undergo further therapies at the treated site. Further studies are required to determine the most cost-effective setting to use this sophisticated technology for vertebral metastases.

While hemibody irradiation can provide rapid pain relief for diffuse painful bone metastases,[53,59] its use is less frequent due to the increasing availability of radionuclide therapy. For predominantly osteoblastic diffuse painful bone metastases, radionuclide therapy has the advantage of treating multiple sites simultaneously.

The currently available radiopharmaceuticals deliver a therapeutic dose of beta radiation and include strontium-89, samarium-153, and phosphorus-32.[60,61] Samarium-153 is currently the most commonly used radionuclide in the United States.[62] These radionuclides concentrate in actively calcifying areas by binding to hydroxyapatite, with a high affinity in metastatic sites, where there is rapid bone turnover. Inhibition of lymphocyte-associated cytokines or alterations in osteoclast or osteoblast activity are thought to be the underlying mechanism for pain relief. Both samarium-153 and strontium-89 have been shown to be effective for palliation of pain from osteoblastic lesions in metastatic prostate or breast cancer, with improvement in pain score and decrease in analgesic intake ranging from 50% to 90%.[63,64] An alpha-emitting radioisotope is another category of radionuclide therapy. It has promising efficacy with minimal myelotoxicity and is currently being actively investigated for clinical use. Details of its use are discussed in a separate article included in this issue (Tomblyn M; pp 137-144).

The side effects of radiopharmaceuticals include bone marrow suppression, which is usually temporary and may be worse in heavily pretreated patients. Nevertheless, at least one report showed that myelotoxicity after radionuclide therapy was not significant in patients who had prior radiotherapy or chemotherapy, and multiple successive samarium-153 therapies can be administered safely with minimal cumulative risk of myelosuppression, as demonstrated by a retrospective review by Heron et al[65] from the University of Pittsburgh.

A recent Cochrane review of published randomized controlled trials concluded that pain relief does not significantly differ among various radionuclides and observed evidence, supporting pain reduction over 1 to 6 months with no increase in analgesic use.[60] This review did find frequent severe adverse effects, including leukocytopenia and thrombocytopenia, after radiopharmaceutical treatment.

Combining EBRT and radionuclides has been shown to be safe.[66] This approach allows effective palliation of both localized and diffuse pain arising from widespread bone metastases. There has been no published randomized trial investigating the efficacy of combining radiotherapy and bisphosphonates. Data emerging from animal and clinical studies showed promising remineralization and restabilization of osteolytic metastases when EBRT was combined with bisphosphonates.[67,68] Combining bisphosphonates with radiopharmaceuticals for improved palliation for patients with osteoblastic metastases from prostate, lung, and breast cancers is another promising approach being investigated in a randomized clinical trial sponsored by the RTOG (RTOG 0517).

Surgery

The goals of surgical management are palliation of pain and functional preservation and restoration. The majority of patients without fracture do not require surgery for bone metastasis. If a pathological fracture of a long bone is present, it is often best treated with internal fixation and instrumentation. Other goals of surgical intervention include immediate weight-bearing and return to activity. Prophylactic fixation of impending pathological fracture may be considered for metastatic disease to the long bone if an osteolytic lesion involves more than 50% of the cortex circumferentially or if metastasis involves the proximal femur with an associated fracture of the lesser trochanter.[28,69] Percutaneous vertebral augmentation with polymethyl methacrylate can be used to optimize spinal stability.[36,37] Both vertebroplasty and kyphoplasty can improve pain in patients who have vertebral body compression fractures that do not cause neurologic deficits.[70] Postoperative radiotherapy is generally given after surgical stabilization; no data suggest surgical stabilization precludes the need for radiotherapy. In select cases, surgery may be considered if localized pain persists despite radiotherapy and analgesic therapy. However, if a patient has a limited life expectancy of weeks to months, nonsurgical alternatives should be considered in lieu of surgical fixation.

Metastatic disease to the vertebrae can result in spinal cord compression or spinal instability, and progressive neurologic deterioration is considered an emergency that requires immediate consideration of surgical intervention.[8] Patchell et al[8] demonstrated that surgical decompression followed by postoperative radiation therapy improved the chance of regaining the ability to walk and of maintaining ambulation compared with radiation therapy alone. Therefore, combined surgery and radiotherapy should be the standard treatment paradigm.

Other indications for surgical intervention include intractable pain and nerve root compromise.[28,71] Vertebral augmentation techniques such as kyphoplasty and vertebroplasty have been shown to be effective for pain relief and may lead to improvement in the mechanical stability of the vertebrae. Patients with an unstable spine who are not candidates for radical surgery may benefit from vertebral augmentation. The presence of retropulsion of bone fragments into the spinal cord is a contraindication for vertebral augmentation.

Conclusions

Management of metastatic disease to the bone is challenging, and intervention is often individualized. Suggested algorithms and pathways for the management of bone metastasis, both vertebral and nonvertebral, are outlined in the Figure. In the majority of patients, treatment of bone metastasis is palliative, and the goals of treatment are to relieve pain, improve function, and prevent complications such as spinal cord compression and pathological fracture. A combination of analgesic/pain management, systemic treatment, radiotherapy, and surgical intervention using a multidisciplinary approach provides the opportunity to optimize treatment goals for each individual patient.

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