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NCCN Task Force Report: Bone Health and Cancer Care

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Task Force: Bone Health and Cancer Care

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Target Audience

This educational activity is designed to meet the educational needs of both oncologists and primary care physicians who provide ongoing care for oncology patients.

Educational Objectives

After completion of this CME activity, physicians should be able to:

- Understand screening and detection of osteoporosis
- Define biomarkers in bone health
- Identify treatment options for osteoporosis
- Recognize chemotherapy-induced ovarian failure
- Understand chemotherapy-induced bone loss
- Recognize appropriate management of skeletal complications of breast and prostate cancer
- Understand the pathophysiology and imaging of bone metastases
- Define surgical management of bone metastases
- Understand management of bone pain related to metastases

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NCCN Task Force Report: Bone Health and Cancer Care

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NCCN Clinical Practice Guidelines in Oncology, bone health, osteoporosis, osteopenia, bisphosphonates, parathyroid hormone, breast cancer, prostate cancer, dual x-ray absorptiometry, aromatase inhibitors, chemotherapy, bone metastases, bone mineral density

Abstract

Higher incidences of osteoporosis and osteopenia are found in cancer patients, particularly in women receiving aromatase inhibitors or with chemotherapy-induced ovarian failure, or in men with prostate cancer and androgen deprivation therapy. Therefore, management of long-term bone health is emerging as an important aspect of comprehensive cancer care. Patients with cancer typically have a number of additional risk factors for osteoporosis that should prompt screening, regardless of patient age or sex. Maintaining bone health requires a broad knowledge base, including understanding

underlying bone metabolism and how it is affected by both cancer itself and the drugs used to treat cancer, the effect of chemotherapy-induced menopause on bone health, bone markers and imaging techniques used to assess bone health, therapeutic strategies to maintain bone health, and treatment of bone metastases, including surgery for pathologic fractures. Multiple members of the healthcare team may need to be involved in education and care of the patient. This report summarizes discussion of these and other issues regarding bone health and cancer care from the NCCN Bone Health and Cancer Care Task Force meeting in early 2006. (*JNCCN* 2006;4(Suppl 2):S1-S24)

Background

Key Points

- Higher incidences of osteoporosis and osteopenia are found in cancer patients, particularly in women

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receiving aromatase inhibitors (AIs) or with chemotherapy-induced ovarian failure, or in men with prostate cancer and androgen deprivation therapy (ADT).

- Management of long-term bone health is emerging as an important aspect of comprehensive cancer care.

In many patients with breast or prostate cancer, cancer can be seen as a chronic disease that requires a focus on long-term comorbidities such as osteoporosis and fracture risk. The morbidity associated with fracture is obviously a concern, but additionally, both vertebral and hip fractures are associated with a 20% decrease in survival over the next 5 years.¹ Osteoporosis and osteopenia are extremely common; experts estimate that 22 million women have osteopenia and 8 million have osteoporosis. More than 2 million American men also have osteoporosis, and about one third of hip fractures occur in men. Chemotherapy and other supportive medications such as corticosteroids can contribute to bone loss. For example, hormone-modifying therapies such as AIs and ADT increase bone loss and fracture risk. The increasing use of AIs and ADT will likely increase the number of cancer patients at increased risk for fracture.

Although screening and treatment of osteoporosis has focused on postmenopausal women, bone health is a critical issue for all cancer patients, regardless of other risk factors, and should be incorporated into comprehensive cancer care. An American Society of Clinical Oncology (ASCO) Task Force statement on bone health in women with breast cancer noted, “Many women with newly diagnosed breast cancer are at risk of osteoporosis because of their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in routine and regular assessment of women’s bone health.”² Unfortunately, many cancer patients, particularly breast cancer patients with chemotherapy-induced ovarian failure or bone loss, do not seem to undergo regular assessment of bone health.³

Maintaining bone health requires a broad knowledge base, including underlying bone metabolism, the effects of both cancer itself and the drugs used to treat cancer, the effect of chemotherapy-induced menopause on bone health, bone markers and imaging techniques used to assess bone health, therapeutic strategies to maintain bone health, and treatment of bone metastases, including surgery for pathologic fractures.

Multiple members of the health care team may be needed for effective patient care and education.

This report summarizes presentations made at the meeting of the NCCN Bone Health and Cancer Care Task Force.

Screening and Detection of Osteoporosis

Key Points

- Patients with cancer typically have a number of additional osteoporosis risk factors that should prompt screening, regardless of age or sex.
- Bone mineral density (BMD) measurements with DXA (dual x-ray absorptiometry) can vary with the instrument used and the anatomic site assessed; therefore, serial monitoring of BMD should be performed on the same piece of equipment using the same reference standards and at the same anatomic site.
- Changes in DXA scan in response to antiresorptive medication typically occur over a long period of time, and serial DXA scans should generally not be performed more than once a year.

The basic facts of normal bone physiology are familiar—bone is constantly turning over and remodeling, with resorption exceeding formation after peak bone mass is achieved by age 30 and with women having a period of accelerated bone loss at menopause. Screening primarily consists of measuring BMD, although physical examination can also suggest the diagnosis of osteoporosis.⁴ The U.S. Preventive Services Task Force recommends screening for osteoporosis in all women older than 65 years or at age 60 for women with increased risk factors such as low body weight (< 70 kg) or low estrogen.⁵ However, as listed in Table 1, a constellation of both modifiable and non-modifiable risk factors or risk factors for secondary osteoporosis may also prompt screening in cancer patients, regardless of age or sex.^{1,6}

Both cancer itself and cancer therapies can have profound effects on bone metabolism. Chemotherapy can have a direct effect on gonadal function or a potential direct effect on bone because of chemotherapy-induced changes in bone metabolism. In addition, supportive medications used in cancer care can cause changes in bone metabolism. For example, dexamethasone is routinely used in high doses in conjunction with adjuvant therapy for breast cancer as an antiemetic

Bone Health and Cancer Care

Table 1 Risk and Risk Factors for Secondary Osteoporosis

Modifiable Risks	Non-modifiable Risks	Causes of Secondary Osteoporosis Related to Cancer	Other Causes of Secondary Osteoporosis
Smoking	Gender (female)	Postmenopausal women of any age receiving aromatase inhibitors ²	Endocrine disorders, i.e. hyperparathyroidism, hyperthyroidism, Cushing's syndrome
Diet, including low calcium and Vitamin D intake	Increased age	Premenopausal women with therapy induced with premature menopause	Inflammatory disorders (including arthritis, bowel disease and pulmonary disease)
Exercise	Race (Caucasian)	Hypogonadism due to orchiectomies or treatment with a GnRH agonists. Hypogonadism uniformly occurs in men with prostate cancer treated with GnRH agonists and generally in women on antiestrogen therapies	Not relevant
Estrogen deficiency*	Low weight (< 126 lb in women) and body mass index	Hematologic malignancies	Neurologic disorders (including immobilization and treatment with antiepileptic drugs)
Poor visual acuity (relating to risk of fall)	Family history of osteoporosis	Glucocorticoid therapy	Other metabolic, nutritional disorders and medication
Risk of falls	History of prior fracture	Radiation therapy	Side effects of medication
Medications and their side effects	Late menarche, early menopause, low endogenous estrogen levels*		
Stress	Co-morbid conditions: endocrine, rheumatologic, gastrointestinal, cancer		

* Modification of estrogen levels may not be appropriate in some patients with cancer, such as breast cancer.

or premedication for taxane therapy and may cause secondary osteoporosis. Radiation therapy can have a direct local effect on bone; for example, chest irradiation and pelvic irradiation are associated with an increased risk of rib fractures and pelvic insufficiency fractures, respectively. Overall, breast cancer is associated with increased rates of osteoporosis and fractures, as shown in several studies:

- Researchers found an annual incidence of vertebral fractures of 2.72% in 352 newly diagnosed breast cancer patients compared with 0.53% in a control group of 776 women.⁷
- The Women's Health Initiative studied the incidence of self-reported fractures among women with and without a history of breast cancer, with an average follow-up of 5 years. The cumulative fracture rate was similar for hip and clinical spine fractures, but postmenopausal breast cancer survivors had a

significantly higher incidence of lower arm and wrist fracture and total fracture.⁸

A variety of different technologies is available for osteoporosis screening, including DXA, peripheral ultrasound and quantitative computed tomography (CT) scanning. However, DXA is considered the gold standard because of its intermediate cost, low radiation exposure, excellent precision, the ability to monitor treatment response, and validation in a large number of clinical trials.

The image of the scanned area (Figure 1) must be carefully reviewed for artifacts that can affect the reported BMD, such as an overlying osteophyte, calcific aorta, compressed vertebral fracture or blastic metastasis. The DXA report includes a graphic representation of the bone mineral density (measured in g/cm²) compared with normal values, which is then translated into a T-score and a Z-score. The T score refers to the number of standard deviations (SD) above or

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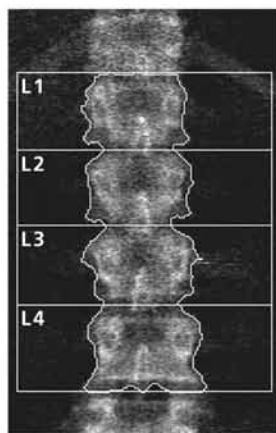
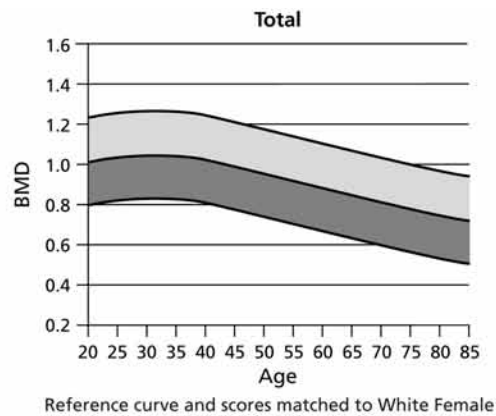


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116 x 145



Reference curve and scores matched to White Female

Patient Information:

Name:	
Social Security No:	
Patient ID:	
Postal Code:	
Sex:	Female
Ethnicity:	White
Height:	70.0 in
Weight:	236.0 lb
DOB:	
Age:	38
Menopause Age:	
Referring Physician:	

Scan Information:

Scan Date:	November 01, 2005 - H11010507
Scan Type:	a Lumbar Spine
Analysis Date:	11/01/2005 11:09
Report Date:	11/01/2005 11:17
Institution:	
Operator:	
Model:	QDR 4500W (S/N47034)
Comment:	

Results Summary:

Region	Area [cm ²]	BMC [(g)]	BMC [g/cm ²]	T-Score	PR (Peak Reference)	Z-Score	AM (Age Matched)
L1	14.53	15.46	1.064	1.3	115	1.4	117
L2	14.66	18.09	1.234	1.9	120	2.0	122
L3	15.57	18.26	1.173	0.8	108	1.0	110
L4	18.30	21.07	1.151	0.3	103	0.5	105
Total	63.06	72.89	1.156	1.0	110	1.1	112

Total BMD CV 1.0%, ACF = 1.004, BCF = 0.972

Fracture Risk: Not Increased; WHO Classification Normal

Figure 1 Example of a typical report from a DXA scan.

below the mean for the young healthy population, and the Z score is related to an age-matched control. Typically, the T score is reported for several anatomic sites, including several sites in hips (proximal femur, femoral neck, and trochanter), several vertebrae (L1-

L4), and occasionally the forearm. For every 1 SD decrease in BMD there is a doubling of the fracture risk, which further increases with age.^{9,10}

In 1994, the World Health Organization established diagnostic criteria for osteoporosis, based on T scores (Table 2). The National Osteoporosis Risk Assessment (NORA) study assessed low BMD and fracture incidence in 200,000 postmenopausal women.¹¹ Based on the WHO definition in this population, 39.6% had osteopenia and 7.2% had osteoporosis. Osteoporosis was associated with a fracture rate approximately 4 times that of women with normal BMD, and the fracture rate was 1.8-fold higher in those with osteopenia. Intervention strategies are typically focused on women with osteoporosis, but these data suggest that women with osteopenia might also benefit from intervention. In a subsequent analysis, Miller et al.¹² concluded that women with a T score lower than -1.8 could be considered at high risk based on information easily gathered in a routine clinic visit; such as a history of prior fracture, fair to poor self-reported health status, or poor self-reported mobility.

Although DXA measurements are considered the gold standard, their limitations must also be recognized. For example, results can vary with the machine used, with the different underlying dual-energy methods used, calibration differences, different detectors

Table 2 WHO Diagnostic Criteria for Osteoporosis

Classification	T score
Normal	-1 or greater
Osteopenia	Between -1 and -2.5
Osteoporosis	-2.5 or less
Severe Osteoporosis	-2.5 or less and fragility fracture

used, different reference standards, and also by anatomic site (e.g., hip vs. vertebrae). These factors explain why serial monitoring of BMD must be performed on the same piece of equipment using the same reference standards. In addition, a T-score of -2.5 should not be interpreted as the definitive cut-off for osteoporosis, which can also be diagnosed in the presence of a fragility fracture, regardless of T score. Conversely, a T score of -2.5 can falsely suggest osteoporosis in the presence of osteomalacia.

Changes in the DXA scan in response to antiresorptive medication typically occur slowly, and in general serial DXA scans are not performed more frequently than at 1-year intervals. However, when accelerated bone loss occurs, such as in the case of hyperparathyroidism or in the bone marrow transplant setting, serial DXA scans at shorter intervals may be warranted.

Other routine imaging studies of the spine can suggest osteoporosis. For example radiographs can provide a qualitative assessment of osteoporosis if the endplates appear more radio-opaque than the vertebral bodies themselves. Osteoporotic compression fractures can also be detected using magnetic resonance imaging (MRI). Future imaging options include multi-slice CT scanners and positron emission tomography (PET)-CT fusion studies, which may be particularly helpful in distinguishing compression fractures from pathologic fractures.

Biomarkers in Bone Health: Normal Bone Physiology

Key Points

- Bone turnover markers provide a complementary approach to measurements of BMD.
- Bone turnover markers can confirm the effect of antiresorptive therapy within 2 to 3 months, com-

pared with 12 to 24 months needed to detect significant changes on DXA scan.

- Lack of change in bone turnover markers after starting antiresorptive therapy may suggest the need to alter therapy or may suggest patient nonadherence.

Bone remodeling is a constant process with tightly coupled and balanced bone resorption by osteoclasts followed by bone formation by osteoblasts. In healthy, mature bone maintenance, these actions are balanced. In disease processes, this balance may tip toward excessive resorption or deposition. Hormones impacting bone metabolism include parathyroid hormone (PTH), calcitonin, estrogen, testosterone, growth hormone, insulin-like growth factor, thyroid hormone, and cortisol. In addition, a whole host of other local factors, including hydrolytic enzymes (collagenase, cathepsins), matrix metalloproteinases, cytokines, and eicosanoids, are present in the bone microenvironment and can be impacted by disease or drug therapy.

Bone loss occurs when bone resorption exceeds bone formation. Increased bone resorption with disease results in accelerated bone loss and associated disrupted trabecular architecture, decreased mineralization density, and reduced bone strength. Given the slow changes in BMD in response to antiresorptive agents, interest is ongoing in measuring byproducts of bone metabolism released into the serum and urine as dynamic markers of the bone remodeling process. Biochemical bone markers can be broadly subdivided into markers of bone formation and bone resorption, thus providing the ability to simultaneously examine both resorption and formation.

Bone Formation

Bone-Specific Alkaline Phosphatase: This isoenzyme of alkaline phosphatase is specific to bone, although there is some cross-reactivity (16%) to liver with the immunoassays used to measure this isoform. Two immunoassays are commercially available, Ostase and Alkphase-B.

Osteocalcin. This protein is synthesized by osteoblasts and incorporated into bone matrix.

Pro-collagen Extension Peptides. These are small peptide by-products of bone collagen synthesis that are released prior to the incorporation of collagen into bone. Monoclonal antibodies have been raised to both the carboxy- (P1CP) and amino- (P1NP) terminal

ends. Elevated levels of these peptides have been associated with metabolic bone disease.

Bone Resorption

Cross-Linked Telopeptides of Type I Collagen (N-terminal [NTx] or C-terminal [CTx]:) In general, pyridium crosslinks are connective structures that bind collagen fibrils together and provide tensile strength to bone. When bone begins to demineralize, these cross-links break, are released into circulation, and can be measured in both the serum and urine. Antibodies to both the N-terminal and C-terminal ends of the pyridinium-linked telopeptides are available and have been fashioned into immunoassays that can measure these telopeptides in health and with metabolic bone disease. Both NTx and CTx can be detected in serum or urine using ELISA or chemiluminescence based techniques.

Measuring Bone Turnover

Many physiologic factors affect the levels of bone markers. For example, bone markers can vary with bed rest, seasonal changes, menstrual cycle, and time of day and are affected by comorbid conditions such as kidney and liver disease, leading to marked physiologic variability ranging from 15% to 40%. Studies have shown that overnight fasting significantly reduces the circadian variation of the CTx markers, and thus a second void urine sample may be optimal for clinical application.^{13,14} Additionally, studies have shown lower physiologic variability for serum markers compared with urine markers.^{15,16}

Changes in bone turnover markers can reflect response to antiresorptive therapy in weeks rather than the months to years required with DXA. Therefore, clinical use of bone turnover markers is focused on monitoring patient response and effectiveness of antiresorptive therapies. The ability to assess response to antiresorptive therapy earlier than a DXA scan allows is helpful in many clinical situations, to avoid the time and expense of a potentially ineffective therapy and to initiate a prompt alternate therapy, such as calcitonin or parathyroid hormone. Additionally, bone turnover markers can be used to assess patient adherence to therapy.

Bone turnover markers can also be used to predict response to therapy. For example, Chestnut et al.¹⁷ compared changes in urinary NTx levels and changes in bone mass in 109 postmenopausal women undergoing hormone replacement therapy. Patients with the highest quartile for baseline levels of NTx and

those with decreasing levels over 6 months also had the largest percentage gain in BMD. Ravn et al.¹⁸ compared short term changes (3-12 months) in urine CTx and other biomarkers to changes in BMD measured after 2 years in postmenopausal patients receiving alendronate. A 50% decrease in CTx had an 87% positive predictive value for predicting prevention of bone loss. Other studies have shown prompt reductions in CTx associated with ibandronate and calcitonin therapy.¹⁹

Update on Treatment Options for Osteoporosis

Key Points:

- Adequate calcium and vitamin D intake and exercise are recommended for primary prevention. Calcium and vitamin D may have a modest role treating older men and women.
- Overall risks and benefits of estrogen therapy suggest that this is not a first-line therapy for osteoporosis for menopausal women.
- Testosterone may improve bone mass and body composition but has not been shown to decrease fracture risk.
- Caution must be exercised regarding hormonal manipulation in patients with a history of cancer.
- Bisphosphonates have been shown to reduce incidence of both vertebral and hip fracture and may be the drugs of choice for cancer survivors.

Initial preventive strategies for osteoporosis consist of adequate intake of calcium and vitamin D. Recommended total daily calcium intake is 1200 to 1500 mg in divided doses, either through diet or supplementation.^{20,21} The recommended daily intake of Vitamin D varies. The USDA recommends 400 to 600 IU (<http://www.nal.usda.gov/fnic/etext/000105.html>), with other experts recommending 800 IU of cholecalciferol (vitamin D3) to achieve a target 25-hydroxyl vitamin D level greater than 32 ng/mL.²² However, data from randomized trials regarding the effect of calcium and vitamin D supplementation on the treatment of osteoporosis are conflicting. For example, in a 1992 study of postmenopausal women who received calcium and vitamin D3 supplementation, the incidence of vertebral and hip fractures was lower in the intervention group, but a large percentage of participants were vitamin

D deficient, so this study really focused on the treatment of osteomalacia rather than osteoporosis.²³ A subsequent 1997 study that included both men and women over 65 reported only a modest increase in BMD with calcium and vitamin D supplementation.²⁴

More recent studies, such as the large RECORD study, reported that calcium and vitamin D supplementation had no impact on the incidence of secondary fracture in a population of 5292 men and women older than 70 with a prior low-impact fracture.²⁵ Similarly, a randomized study of postmenopausal women with additional risk factors for fracture found no significant reduction in fracture incidence in those receiving calcium and vitamin D supplementation.²⁶ The large Women's Health Initiative, with more than 36,000 women between the ages of 59 and 70, also included an arm in which women received calcium and Vitamin D supplementation. However, one conclusion of the available studies is that calcium and vitamin D supplementation alone is probably not adequate to reduce fracture risk. Results of this study are pending and may further clarify the role of supplementation.²⁷

Antiresorptive agents have been an important research focus for the past 20 years. This category includes drugs like estrogen, bisphosphonates, calcitonin, the selective estrogen receptor modulators (SERMs) and strontium. All the antiresorptive drugs function by decreasing bone turnover, which may lead to a preservation of bone architecture or an increase in BMD, or both, ultimately leading to a reduced fracture rate. Randomized, placebo-controlled studies of antiresorptive agents have generally focused on vertebral fracture rates, primarily because the increased incidence compared with hip fracture makes them easier to study. Of interest is that a very consistent decrease is seen in relative risk for fracture for a variety of antiresorptive agents, but the increase in BMD is variable. In a review of 12 randomized trials of antiresorptive agents, Cummings et al.²⁸ reported that changes in BMD only explained a small portion of the observed decrease in fracture risk. For example, in the Fracture Intervention Trial of alendronate, the improvement in spine BMD explained only 16% of the reduction in the risk of vertebral fracture. Therefore, although changes in BMD are a reasonable surrogate outcome, trials with fracture outcomes are required to demonstrate treatment efficacy. However, of note, studies have focused on postmenopausal women, and

randomized studies using fracture endpoints have not been conducted in cancer patients without known metastatic disease.

Given the few head-to-head studies of different antiresorptive agents, the choice among the available treatment options often focuses on treatment side effects and patient co-morbidities. For example, although the Women's Health Initiative study showed that estrogen alone or combined estrogen and progesterone therapy were associated with a 33% to 34% reduction in hip fracture, the ubiquity of estrogen receptors in other tissues leads to unacceptable side effects, such as an increased incidence of cardiovascular disease. Raloxifene is currently the only SERM that has been Food and Drug Administration (FDA) approved for the prevention and treatment of osteoporosis. Although raloxifene has been shown to decrease the incidence of vertebral fracture, randomized studies have failed to document any benefit in terms of non-vertebral or hip fractures.²⁹ However, a possible advantage of SERMs compared with estrogen therapy is the lack of early increase in coronary heart disease and a significant reduction in hormone receptor-positive breast cancer. Results of the ongoing STAR trial (Study of Tamoxifen and Raloxifene) comparing raloxifene and tamoxifen as breast cancer chemopreventive agents are eagerly awaited.

Other than hormonal therapy, the only drugs that have been shown to decrease the incidence of both vertebral and hip fractures are bisphosphonates, which are available in a variety of formulations, including daily, weekly, and monthly oral doses and intravenous doses for those who cannot tolerate oral agents. Alendronate has been shown to significantly reduce the incidence of hip fracture as early as 18 months after the start of therapy.³⁰ Risedronate was also associated with a significant reduction in the incidence of hip fracture in a population of women older than 70 with osteoporosis.³¹ However, in a subgroup of women over the age of 80, selected only on the basis of non-skeletal risk factors for fracture (prior fall, cigarette smoker), no significant reduction in hip fracture risk was seen. The reasons for this discrepancy are not clear, but it may illustrate the multifactorial nature of fracture risk.

Ibandronate is a relatively new bisphosphonate; studies with hip fracture outcomes are not available for this agent, but research showed a daily formulation to be associated with a 62% reduction in the risk of vertebral fractures.³² Evidence also suggests that

intravenous pamidronate or ibandronate, given every 3 months, has beneficial effects on bone density in women with postmenopausal osteoporosis.^{33,34}

Pamidronate has been studied specifically in patients with chemotherapy-induced ovarian failure.³⁵ In a randomized trial of 40 premenopausal women with newly diagnosed breast cancer, pamidronate prevented bone loss at the spine and hip. In this trial, the dosage of pamidronate was 60 mg intravenously every 3 months, compared with the typical dose for postmenopausal patients of 30 mg intravenously every 3 months. In fact, studies of bone loss in women with breast cancer consistently show that bisphosphonate therapy can maintain bone density of the spine, with a slowing of bone loss at the hip.³⁶ Bisphosphonates have also been shown to prevent bone loss in men with prostate cancer undergoing ADT.^{37–39} However, no studies have evaluated fracture outcome data in cancer patients without metastatic disease. In patients with bone metastases, bisphosphonates have been shown to reduce the frequency of fractures.^{40–44}

PTH (teriparatide) is distinct from bisphosphonates because it not only increases bone density but also increases bone formation. Therefore, unlike bisphosphonates, with which bone turnover markers decrease, PTH therapy is associated with an initial increase in bone formation markers. In a randomized study of postmenopausal women with prior vertebral fractures, PTH was associated with significant reduction in both vertebral and nonvertebral fractures.⁴⁵ Contraindications to PTH include prior radiation therapy of the skeleton and hypercalcemia. Metastatic disease is also a contraindication because, theoretically, PTH can activate micrometastatic disease in the marrow. Because of the potential association of breast cancer with occult, micrometastatic bone involvement, PTH is generally not considered an option for breast cancer patients.⁴⁶

Strontium ranelate is currently under investigation as a treatment for osteoporosis. This drug functions by uncoupling bone resorption from bone formation, allowing a suppression of bone resorption and unimpeded bone formation. Results of two randomized studies were reported: Meunier et al.⁴⁷ noted that the drug was associated with a decreased incidence of vertebral fractures in postmenopausal women with osteoporosis, and Reginster et al.⁴⁸ reported that the drug was associated with a decreased risk of nonvertebral fractures.

Tamoxifen is a commonly administered agent in patients with breast cancer. Although it has antiresorptive properties, it is not an adequate treatment for osteoporosis. It is associated with increased bone density in the lumbar spine; however, it also shows non-significant effects in the femoral neck in postmenopausal patients, and reduced BMD in premenopausal patients.^{49,50}

Emerging insights into the microenvironment of bone metabolism have identified new therapeutic targets for maintaining bone health. For example, osteoclastogenesis refers to development of osteoclasts from precursor macrophage/monocyte cells. Recently, it was discovered that this complex process is under the control of proteins that have been characterized. For example RANK-L (receptor activator of nuclear factor κ B ligand) is an essential cytokine that is expressed on the surface of preosteoblastic and osteoblastic cells. RANK-L activates its receptor RANK, which is expressed on osteoclasts and their precursors, ultimately promoting osteoclast formation and activation. The effects of RANK-L are blocked by osteoprotegerin (OPG), which acts as a decoy receptor for RANK-L. The balance among RANK, RANK-L, and OPG is in turn regulated by a variety of cytokines and hormones; alterations in this balance are found in a variety of diseases associated with bone resorption.⁵¹

Drugs targeting this pathway are now under development. Bekker et al.⁵² reported on a preliminary study of AMG 162 (denosumab), a human monoclonal antibody to RANK-L, in 49 postmenopausal women. They found profound reductions in the urinary bone turnover marker NTx, which were maintained over 6 months with a single subcutaneous dose.⁵² McClung et al.⁵³ reported that denosumab use in postmenopausal women increased BMD at the lumbar spine and total hip. The study was a randomized comparison of denosumab, alendronate, or placebo with denosumab showing an improvement in BMD. This novel monoclonal antibody therapy is in clinical trials for both osteoporosis and bone metastases.

Chemotherapy-Induced Ovarian Failure

Key Points:

- Chemotherapy-induced ovarian failure with associated estrogen deprivation is one of the most prevalent long-term side effects of adjuvant chemotherapy for breast cancer, and results in increased bone loss.

- Temporary chemotherapy-induced ovarian failure must be carefully distinguished from menopause, because adjuvant use of aromatase inhibitors is only indicated in the absence of ovarian estrogen production.
- Bisphosphonate therapy can attenuate the bone loss associated with ovarian failure; however, to date, data on changes in the rate of fracture are insufficient.

Chemotherapy-induced ovarian failure and early menopause are common side effects of adjuvant therapy for breast cancer, occurring in 50% to 70% of pre- or perimenopausal patients treated with chemotherapy and resulting in an increased risk of osteopenia or osteoporosis. The most important factor for predicting the risks of ovarian failure or menopause is patient age at time of treatment, with an increasing risk with increasing age.⁵⁴ Additional factors include the chemotherapy regimen used.^{55,56} One of the challenges in studying this issue is the lack of standard definitions. For example, some studies defined chemotherapy-induced ovarian failure as amenorrhea longer than 3 months, but temporary amenorrhea does not have the same clinical implications as permanent ovarian failure or menopause. A more stringent definition of menopause is 12 or more months of amenorrhea, with a follicle-stimulating hormone (FSH) level ≥ 30 MIU/mL and a negative beta human chorionic gonadotropin (B-HCG) level. The diagnosis of menopause has significant implications for endocrine therapy in breast cancer patients. For example, AIs are only indicated for postmenopausal patients, and clinicians must not confuse temporary chemotherapy-induced ovarian failure with menopause.

Several small studies have begun to identify risk factors for chemotherapy-induced ovarian failure. For example, in a multivariate analysis of 49 patients, a higher baseline BMD increased the risk of ovarian failure. Specifically, as total spine BMD at baseline increases by 0.1 g/cm², the odds of developing chemotherapy-induced ovarian failure increase by sixfold.⁵⁷ Serum inhibin is a protein produced by the ovarian granulosa cells, and in a study of 63 premenopausal breast cancer patients receiving anthracycline or taxane chemotherapy, decreases in the subunits A and B were predictive of chemotherapy-induced menopause.⁵⁸

The consequences of ovarian failure after adjuvant chemotherapy were studied by Shapiro et al.⁵⁹

in a prospective study of 49 young women with breast cancer receiving adjuvant chemotherapy. Serial measurements of FSH, BMD by DXA, and bone turnover markers were performed. In this study, 35 women experienced chemotherapy-induced ovarian failure, defined as more than 6 months of amenorrhea, an FSH level greater than 30 MIU/mL, and a negative pregnancy test. In patients with ovarian failure, a highly significant bone loss was seen in the lumbar spine by 6 months, but no significant change was seen in patients who retained ovarian function. Other studies have also reported similar levels of bone loss associated with chemotherapy-induced ovarian failure.⁶⁰⁻⁶²

Several small studies of bisphosphonate therapy in patients with chemotherapy-induced ovarian failure reported that risedronate, clodronate, and pamidronate can attenuate bone loss.^{35,61,62} However, outcomes are primarily reported as changes in BMD, though a more clinically relevant outcome may be change in T score. Also, as noted earlier, no studies in this population have been powered to detect changes in final health outcomes, such as fracture rates.

Aromatase Inhibition-Induced Bone Loss In Breast Cancer and Its Treatment

Key Points:

- Large randomized studies of AIs consistently show that they are associated with increased fracture risk.
- Despite improvements in BMD and T scores with bisphosphonates, studies have not been powered to show improvement in the clinically relevant outcome of fracture incidence.
- Ongoing clinical trials are investigating bisphosphonate therapy for reducing the incidence of bone metastases.

Randomized studies have now established the role of AIs as the adjuvant therapy of choice in postmenopausal women with hormone receptor-positive breast cancer.⁶³ However, these studies also have shown a significant increase in the incidence of fractures in patients treated with AIs compared with tamoxifen (11.0% vs. 7.7%). The BIG 1-98 trial compared adjuvant therapy with tamoxifen and letrozole alone.⁶⁴ As with the ATAC Trial, significant improvement in disease-free survival but also increased incidence of bone fracture were seen with the AI (5.8% vs. 4.1%). The Intergroup Exemestane study compared adjuvant

tamoxifen for 5 years with initial adjuvant tamoxifen followed by exemestane, with a significant improvement in disease-free survival reported.⁶⁵ Exemestane is a steroidal AI with androgenic properties, and thus it was expected that there would be a decreased incidence of osteopenia and osteoporosis. However, the incidence of osteoporosis was significantly higher (7.4%) in the exemestane group compared with the tamoxifen group (5.7%), resulting in a nonsignificant increase in the fracture rate.⁶⁶ The MA-17 trial compared either letrozole or placebo after an initial 5 years of adjuvant tamoxifen.⁶⁷ The design of this trial allowed for a more direct look at the effect of AIs on bone without the confounding factor of concurrent tamoxifen present in the other large randomized studies. The incidence of osteoporosis was 5.8% in the letrozole group compared with 4.5% in the placebo group. As a group, these trials suggest that issues of osteopenia and bone fracture will become more important as AIs are adopted into routine clinical practice.

Two large randomized clinical trials of intravenous bisphosphonates in women receiving AIs are underway. The Austrian Breast Cancer Study Group-12 (ABC SG-12) trial investigates the role of AI therapy in young women who have undergone chemical ovarian ablation with goserelin. These women received initial ovarian ablation with goserelin therapy after surgery and radiation and were then randomized to receive tamoxifen or anastrozole, with or without zoledronic acid.⁶⁸ A bone sub-study was conducted in a subgroup of 401 of the total 1800 premenopausal patients, with 36 months follow-up. The women who did not receive zoledronic acid experienced a 1.4 SD drop in T score compared with the zoledronic acid group. Although changes in BMD and T scores are commonly accepted surrogate markers, ultimately fracture data are optimal for determining clinical significance. In fact, in this study with limited follow-up, no fractures were seen.

Another study is the Z-FAST trial, which randomized 602 postmenopausal women with stage I to III breast cancer treated with adjuvant letrozole to either receive upfront zoledronic acid every 6 months or to a delayed treatment group that received zoledronic acid therapy if the BMD dropped below -2 SD, if there was any clinical fracture, or if an asymptomatic fracture was detected at 36 months.⁶⁹ At 12 months, the immediate treatment group had a 2% increase in BMD, while the delayed group had a 2% de-

crease. This translated to a 30% improvement in T scores in the immediate treatment group. Of those women with an initially normal T score, 20% became osteoporotic at 1 year, and 20% of those with initial osteopenia became osteoporotic. Bone turnover markers were significantly decreased in patients receiving upfront zoledronic acid. Although fracture endpoints are not available, it is interesting to note that the changes in BMD and T score in those receiving letrozole alone are similar to those seen in the ATAC study with anastrozole alone, where the 5-year data confirmed an increase in the fracture rate.

Another randomized clinical trial exploring the effects on bone caused by breast cancer therapy with adjuvant AI treatment in postmenopausal women is the SABRE trial. In this international study, postmenopausal women with early-stage breast cancer receiving adjuvant anastrozole are stratified by BMD and followed up over 2 years for markers of bone turnover and BMD. Those with a T score of -1 or greater receive calcium and vitamin D supplementation. Those with a T score less than -1 to -2 receive calcium and vitamin D and are randomized to receive either risedronate 35 mg weekly or placebo. Individuals with a T score less than -2 are treated with calcium, vitamin D, and risedronate. The study has met accrual, and the first analysis is anticipated in 2006.

Bisphosphonate therapy has also been investigated as a means to reduce bone metastases. As discussed further below, the bone microenvironment contains numerous cytokines that are released with bone turnover. These cytokines can contribute to a favorable environment for bone metastases. Therefore, antiresortive agents may break this vicious cycle. Clodronate, not commercially available in this country, has long been studied in this role. In a study initiated in 1989, 1069 women with stage I to III breast cancer were randomized to receive clodronate or placebo for 2 years. At 5-year follow-up, clodronate was associated with a 31% decrease in bone metastases and a 23% increase in overall survival.⁷⁰ These provocative results have not been confirmed in other trials and the issue is now under further study in the NSABP B34 trial, in which 2200 patients with early-stage breast cancer have been randomized to clodronate or placebo for 3 years after adjuvant chemotherapy. Additionally, a large Intergroup study (SWOG 0307) is currently recruiting 6000 women with stage I to III breast cancer who will be randomized to

receive zoledronic acid, oral clodronate, or oral ibandronate (www.clinicaltrials.gov/ct/show/NCT00127205?order=1). Given the low risk of metastases with current adjuvant therapy, any improvement in the incidence of bone metastases may not be apparent for 6 or more years.

Management of Skeletal Complications of Prostate Cancer

Key Points:

- Osteoporosis is common in men, and treatment-related hypogonadism further increases bone loss.
- Bisphosphonate therapy can reduce the bone loss associated with hypogonadism and complications related to osteolysis metastases
- Zoledronic acid decreases the risk of skeletal related complications in men with androgen-independent prostate cancer and bone metastases.

Although the emphasis on screening for osteoporosis has focused on postmenopausal women, osteoporosis is also common in men, occurring in more than 2 million American men. Among common causes of secondary osteoporosis is hypogonadism related to GnRH agonist therapy in men with metastatic prostate cancer. For example, Mittan et al.⁷¹ examined the effects of GnRH analogue treatment on bone loss and bone resorption in men with prostate cancer compared with age-matched control subjects. After 12 months of GnRH therapy, a significant decrease was seen in BMD of the total hip and ultra distal radius in men receiving GnRH compared with the control group.

The SEER-Medicare database has also provided data regarding the risk of fracture after androgen deprivation for prostate cancer.⁷² This database of approximately 50,000 men with prostate cancer revealed that the frequency of any fracture was significantly higher in those receiving ADT compared with those not receiving anti-androgen therapy. The Medicare Fracture Study was a claims-based cohort study of 10,617 men with prostate cancer treated with GnRH agonist compared with 7774 men with nonmetastatic prostate cancer matched for age, race, geographic location, and comorbidity who were not treated with GnRH agonists.⁷³ GnRH agonist use was associated with a faster time to fracture and a significantly in-

creased risk for any clinical fracture, hip fracture, and vertebral fracture. Although the decrease in BMD certainly contributes to fracture risk, GnRH therapy and disease-related problems may be associated with other adverse factors.

Several randomized studies have focused on bisphosphonate therapy in hypogonadal men with prostate cancer using BMD endpoints. For example, intravenous pamidronate and zoledronic acid given once every 3 months and once yearly are associated with significant improvements in BMD of the spine and hip compared with control groups.^{37,39} Medical or surgical castration creates an estrogen-deficient state, which may contribute to bone loss. SERMs may also have a role in prostate cancer. A randomized trial of raloxifene has shown significant increases in BMD of the hip.⁷⁴

Although radiographically observed metastases from prostate cancer tend to be osteoblastic rather than osteolytic in nature, an osteolytic component is frequently present. This is evidenced by high levels of urinary NTx, indicating high bone turnover, which is a risk factor for skeletal related events, disease progression, and death.⁷⁵ These observations form the basis of osteoclast-targeted therapy such as bisphosphonate therapy in patients with metastatic disease. The pivotal trial of bisphosphonates in men with hormone refractory prostate cancer focused on the role of zoledronic acid, focusing on the incidence of skeletal related events.⁴⁰ A total of 643 men were randomized to receive either placebo or zoledronic acid every 3 weeks; the final endpoint in the trial was skeletal related events (SREs), defined as radiation to bone, pathologic fracture, spinal cord compression, surgery to bone, or change in antineoplastic therapy. Zoledronic acid was associated with an immediate, durable, and significant decrease in bone turnover markers, specifically NTx. After 24 months, zoledronic acid was also associated with a significant decrease in the proportion of patients with SREs. Zoledronic acid also delayed the time to first SRE by about 5 months compared with placebo.

Similar to patients with breast cancer, bisphosphonates have also been studied for reducing the incidence and progression of bone metastases. Dearnaley et al.⁷⁶ reported on the results of a trial of men with newly diagnosed metastatic prostate cancer who were randomized to receive either placebo or clodronate in conjunction with hormonal therapy. The primary

endpoint of the trial was symptomatic end to bone progression-free survival (BPFS), defined as either symptomatic bone metastases or death from prostate cancer. Unfortunately, no significant difference in BPFS between the 2 groups was seen. The CALGB 90202 trial is further studying this issue in 680 men with newly diagnosed prostate cancer. Patients are randomized to receive either initial zoledronic acid or placebo, with cross over to zoledronic acid at progressive disease or SRE.

Pathophysiology of Bone Metastases

Key Points:

- Through cell signaling between the tumor and the bone microenvironment, a cascade of growth factors promote a vicious cycle that perpetuates skeletal metastases.
- Co-expression of osteolytic and osteoblastic factors can produce a mixed pattern of metastases.
- Transforming growth factor beta (TGF- β), produced by tumor cells and released from bone matrix, is a major factor in osteolytic tumor metastases.
- Preclinical studies of inhibitors of TGF- β have shown promise in reducing osteolytic disease. Other drugs in development include inhibitors to RANK-L.

Although bone metastases are broadly classified as either osteoblastic or osteolytic, metastatic disease will typically show a mixture of lesions; additionally, the morbidity associated with the 2 subtypes is similar. At the cellular level, multiple intertwining pathways exist in which the tumor cells interact with osteoclasts, osteoblasts, and the bone matrix. The bone matrix is a storehouse for a variety of bone growth factors, which are released during bone resorption. These growth factors enrich the local microenvironment and can then feed back on the tumor cells, initiating a vicious cycle.

Tumor cells from various primary tumors can produce interleukin-8 or tumor necrosis factor- α , which directly stimulate osteoclasts leading to lytic lesions. Additionally, tumor cells can also indirectly stimulate osteoclasts through the production of such factors as PTHrP or interleukin-11, which act on the osteoblasts to increase the production of RANK-L and decrease the production of OPG, further stimulating osteoclastic bone resorption. As the osteoclasts resorb bone,

TGF- β is released from the matrix. TGF- β , also directly produced by tumor cells, further stimulates the production of further osteolytic factors and stimulates factors that act on other components of the metastatic cascade, such as angiogenesis. Preclinical studies have shown that TGF- β stimulates a number of growth factors in cancer cells that promote metastases. For example, in an animal study, Kang et al.⁷⁷ selected a population of tumors cells that were highly metastatic. A gene array analysis of these cells showed that a number of factors were up-regulated, including RANK-L, interleukin-11, and connective tissue growth factor. All of these genes have an effect on bone cells, and several are regulated by TGF- β . These and other studies suggest that TGF- β may be a therapeutic target; preclinical studies have suggested that blocking TGF- β may reduce metastases not only in bone, but also in other organs.⁷⁸⁻⁸¹

Initial *in vitro* studies have shown that inhibition of TGF- β decreases factors thought to be important for metastases and decreases TGF- β production by the cancer cells themselves. Further, *in vivo* studies in mouse models have shown reduced osteolytic disease when TGF- β was used as a treatment of established metastases and as a preventive therapy before inoculation with tumor cells.⁸²⁻⁸⁴

Tumor cells can also produce many factors that stimulate osteoblasts, including endothelin-1. For example, endothelin-1 is produced in prostate cancer cell lines and osteoblastic breast cancer cell lines; and plasma levels are elevated in men with advanced prostate cancer. Endothelin-1 is a family of 3 vasoactive peptides that bind to 2 different receptors, endothelin A and B receptor. Preliminary animal studies of ABT-627, an endothelin A receptor antagonist (ETAR), have shown that the drug can block new bone formation but has no effect on tumor progression in soft tissues.⁸⁵ Simultaneously, phase II studies showed that, in patients with metastatic hormone-refractory prostate cancer, atrasentan, another ETAR, was associated with increased time to tumor progression in bones and reduced markers of bone remodeling.^{86,87} A phase III trial of atrasentan in men with hormone-refractory metastatic prostate cancer was stopped prematurely because of the lack of improvement in overall disease progression, although a subset analysis of patients with bone metastases showed that the drug was associated with a significant reduction in progression of bone disease.

Although prostate cancer is characterized by osteoblastic lesions, osteolytic lesions are an equally important contributor to skeletal morbidity. These patterns suggest that treatment approaches must incorporate combined treatment that can block both osteolysis and osteoblastogenesis. Possible treatment approaches include combined treatment with ETAR and bisphosphonates such as zoledronic acid. Mouse studies using an osteoblastic cell line have shown that either drug given alone can reduce osteoblastic metastases, but the combination of both drugs has a significant additional benefit. Another research interest is examining how increased bone resorption, seen with both ADT and AIs, can affect bone metastases by increasing the release of cytokines from the bone matrix. For example, in a study of castrated mice inoculated with a tumor cell line, treatment with zoledronic acid decreased bone metastases.⁸⁸

Imaging of Bone Metastases

Key Points:

- Interpreting imaging modalities for bone metastases requires simultaneous review of all relevant imaging studies with full clinical context.
- Unlike in bone survey or scintigraphy, both PET scans and MRI show bone marrow but not the bone itself. Therefore, lesions present on MRI or PET may not be visible on bone scans, and vice versa.
- Monitoring bone metastases is problematic with any imaging technique, including MRI, because changes in bone occur very slowly.

Numerous imaging modalities are used to evaluate bone metastases, including plain radiography, skeletal scintigraphy, CT scan, MRI, PET, PET-CT fusion, and CT with multiplanar single-photon emission CT (SPECT). Even with these options, however, distinguishing benign from malignant processes may be difficult. Thus, the ability to review all studies simultaneously to take advantage of complementary information is important. Simultaneous review can be facilitated with a picture archive and communication system (PACS). Ideally, the electronic medical record can be accessed from the imaging station so that the images can be easily analyzed with the full clinical context of the patient.

Skeletal scintigraphy is typically the first-line imaging modality for patients with suspected metastatic

breast cancer. Sensitivity is estimated at between 62% and 100%, with the lowest sensitivity seen in patients with active lytic disease. Specificity is estimated between 78% and 100%, with lower specificity associated with the common co-morbidities of arthritis or trauma. Skeletal scintigraphy is also used to monitor response, as noted by a change in intensity of existing lesions. An increased number of lesions or an increased intensity of lesions signals progression when disease “flare” (seen with initial response) can be ruled out. Disease flare with treatment can be particularly problematic. For example, an inconspicuous lesion may only become apparent with disease flare and may be misinterpreted as a new lesion.

Bone surveys are another common technique for disease monitoring, although the sensitivity is low (44%–50%) and specificity is unclear. The value of bone surveys is related to the detection of lytic and blastic changes over time and the ability to distinguish arthritic changes from metastatic disease. However, because bone changes occur very slowly, repeat bone radiographs at 2-month intervals are unlikely to show meaningful or significant change.

MRI is associated with a high sensitivity (82%–100%) and specificity (73%–100%) for bone marrow metastases. Treatment response on MRI is indicated by a decreased T2 signal, decreased contrast enhancement, or a decreased T1 signal in the case of blastic lesions. Progression is noted by increased bulk or new lesions. PET-CT scans have mixed sensitivity (62%–100%) with high specificity (96%–100%). The main value of PET-CT is the detection of metabolically active bone disease. Physicians should also remember that unlike bone survey or scintigraphy, both PET scans and MRI show the bone marrow and not the bone itself. Therefore, lesions present on MRI or PET may not be visible on bone scans, and vice versa.

Imaging analysis for breast metastases is focused on the most likely bones of involvement: vertebrae, pelvis, ribs, skull, femur, and humerus. Figure 2 illustrates an algorithm of imaging for breast cancer. As the figure suggests, patients with suspected bone metastases should be assessed initially with skeletal scintigraphy.⁸⁹ A positive scintigraph is followed by radiographs to further localize and characterize the lesion. If radiographs are negative and the patient still has symptoms or a suspicious lesion, an MRI or CT scan can be considered. Monitoring bone metastases can be problematic with any imaging technique,

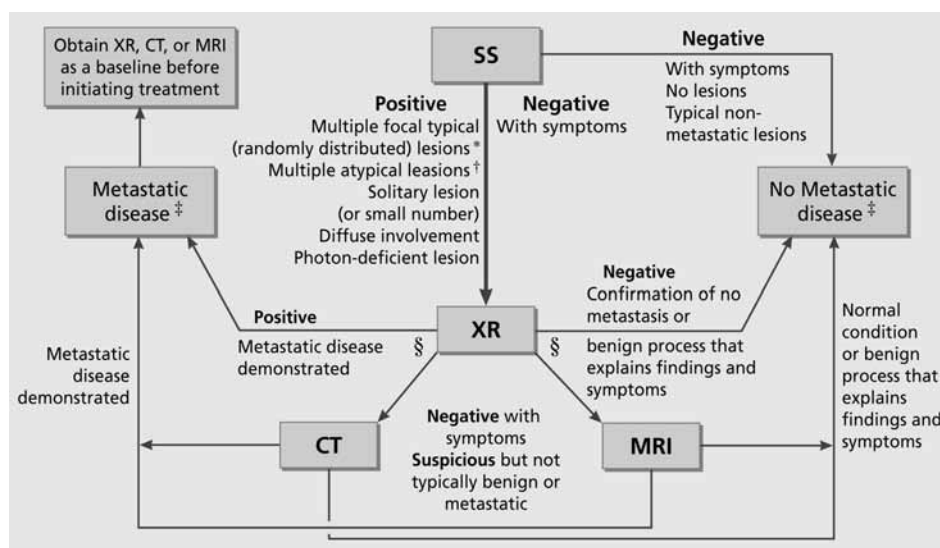


Figure 2 Algorithm illustrating imaging for breast cancer. Reprinted from Hamaoka et al.⁸⁹ with permission.

including MRI, because changes in bone occur very slowly. Additionally, marrow regeneration in successfully treated patients may appear to be progressive disease on MRI or PET. For evaluation of impending fracture and the need for surgical intervention, bone scans and MRI are not helpful, and impending fracture is best evaluated with plain films or CT scans.

The inability to accurately follow bone lesions is one reason that patients with bone metastases are generally excluded from clinical trials unless they have measurable disease in other locations. Some attempts have been made to perform quantitative analysis with serial MRI; however, to date this technique has not been applied clinically. Other imaging options include SPECT-CT scans, in which the SPECT image is fused to a thin slice CT image so that cross-sectional CT images are correlated directly with bone scan images.

Surgical Management of Bone Metastases

Key Points:

- Careful patient selection is critical to successful surgical management of metastatic disease.
- Key patient selection criteria include a readily identifiable source of bone pain, presence of other skeletal metastases that could impact rehabilitation, comorbidity, and life expectancy, all of which must

be balanced against the morbidity of the surgical procedure.

- Treatment of impending pathologic fractures is preferable to treating a pathologic fracture itself.
- Surgical techniques for treatment of traumatic fractures cannot be directly extrapolated to pathologic fractures.

Surgical management of bone metastasis is performed primarily to relieve pain and provide stabilization, and treatment of the local tumor itself typically

involves postoperative radiation therapy. Although surgical treatment of pathologic fractures is often straightforward, treatment of patients with impending pathologic fractures is preferable. For example, compared with treatment of fractures of the femur, treatment of impending fractures is associated with a shorter hospital stay, a greater likelihood of discharge to home versus extended care, and a greater likelihood of support-free ambulation.⁹⁰ Some researchers have attempted to create formal scoring systems to identify patients at risk of impending fracture,⁹¹ but most surgeons identify high-risk lesions based on general criteria: lytic lesions greater than 2.5 cm in diameter, encompassing more than 50% of the bone diameter, or the presence of lesser trochanter avulsion. Additionally, to be considered for surgery, patients should have a life expectancy of at least 6 weeks, particularly if undergoing femoral nailing because of the greater morbidity associated with the procedure. However, these general guidelines must be interpreted and revised in the specific clinical context. For example, arthroplasty would only be considered in patients with longer life expectancy because of the prolonged recovery and rehabilitation. Furthermore, fracture stabilization must be preceded by an assessment of metastatic disease in other bones, which could compromise rehabilitation. For example, when considering stabilization of a femoral fracture, a long bone survey or a bone scan within 2 to 3 months is recommended to detect disease that may relate to weight bearing.

Other indications for surgery for impending fractures include a lesion in a weight bearing area and a readily identifiable painful lesion that is refractory to external beam radiation therapy. It is also important to verify that the lesion is clearly the source of pain. This may be difficult if a patient has multiple sources of pain, such as from osteoarthritis or back pain. Preoperative assessment should include estimation of life expectancy, mental status, mobility status, pain level, metabolic status, skin condition, and nutritional status. Physicians should note that the widespread use of bisphosphonate therapy has resulted in a decrease in the incidence of fracture and that potential fracture may be averted with prompt use of antiresorptive agents, particularly the more potent, rapidly administered drugs.

From a technical standpoint, one of the easiest bones to stabilize is the proximal femoral shaft, while stabilization is more challenging in the pelvis- acetabulum, spine, and periarticular areas. Treatment options include hemiarthroplasty for disease involving the femoral neck or proximal femur and intramedullary nailing for lesions in the subtrochanteric region or in the shaft of the femur. In hemiarthroplasty, long-stemmed prostheses should be used to avoid possible recurrence that would require difficult revision with short-stemmed prosthesis.

Insertion of intramedullary nails is a relatively straightforward procedure that requires either general or regional anesthesia and a hospital stay of about 2 days. Case series of patients treated with intramedullary nailing have reported good outcomes, with complete pain relief and resumption of ambulation in a large proportion of patients. However, these outcomes are in large part related to careful patient selection criteria and appropriate technique.^{92,93} For example, a sliding hip screw is commonly used in patients with osteoporotic fractures of the trochanter. However, these devices are not effective in patients with pathologic fractures, because of the lack of bone healing, particularly with bone radiation.

Stabilization of acetabular disease is technically challenging but is generally done with a variation of hip replacement. Marco et al.⁹⁴ reported on a case series of 55 patients who were treated with curettage of the tumor, protrusion cup, cement, and pin or screw fixation. Although 76% of patients had a decrease in narcotic usage and half of the nonambulatory pa-

tients regained the ability to walk, the authors had a 22% complication rate. Saddle prosthesis is another option; a case series of 20 patients showed a similar improvement in analgesia, independence, and ambulation as reported by Marco. Again, however, the complication rate was high at 20%.⁹⁵ This increase in morbidity underscores the importance of patient selection for extensive surgery.

Stabilization of the humerus is technically straightforward, with the exception of the proximal sixth or distal fourth. Humeral shaft metastases are often treated with locked intramedullary nailing or, more recently, an inflatable nail, with similar outcomes of excellent pain relief and regained use of the extremity in several days.^{96,97}

Despite the widely accepted practice of surgical management of metastatic disease, outcomes analysis is limited because of the absolute lack of controlled trials and limited number of prospective studies. Prospective studies are further limited by the heterogeneous population of patients, the large attrition rate caused by death and loss to follow up and the insensitivity of standard measures in this population of sick and symptomatic patients.⁹⁸ In 2005, Talbot et al.⁹⁹ reported on the results of a prospective study of 67 patients treated surgically for nonspinal metastatic disease. Intramedullary nailing was performed in 36 patients, prosthetic replacement in 24 patients, and plating in 5 patients. With an average postoperative survival of 8 months, functional status improved, but no improvement in the short form (SF)-36 score or decrease in the number of patients using pain medication was seen. However, interpretation is limited because of early and unexpected deaths and a high rate of loss to follow up.

Most literature on this subject consists of retrospective studies from single centers, which in general report improvement in function and pain and a relatively low long-term survival. Dijkstra et al.¹⁰⁰ reported on a case series of 199 patients with 233 long bone fractures treated surgically. Of patients with a 55% 6-month survival rate, 90% reported pain relief, and 76% of those with lower extremity fractures resumed ambulation.

A variety of minimally invasive techniques is also available, including radiofrequency ablation (RFA) and percutaneous osteoplasty, also referred to as cementoplasty. RFA has been used to treat painful bony metastases; Goetz et al.¹⁰¹ reported on a multicenter prospective study in which 43 patients, the majority

of whom had undergone prior radiation therapy, had significant pain relief and reduction in opioid use with minimal side effects. Percutaneous osteoplasty is a technique to improve the mechanical stability of a bone by injecting polymethyl methacrylate (PMMA) cement into a bone lesion using CT or fluoroscopic guidance. The technique has primarily been investigated in the acetabulum and pelvis where other surgeries are technically more difficult. Several small case series have reported reduced pain and improved mobility in most patients.¹⁰²⁻¹⁰⁴ One technical concern with this technique is preventing cement leakage. In the study by Weill et al.,¹⁰⁴ 2 of 18 patients had increasing pain related to cement leakage around the sacral nerve.

Percutaneous vertebroplasty and kyphoplasty describe the injection of cement into fractured vertebral bodies. Kyphoplasty additionally uses a bone tamp that is inflated before the procedure to create a space for injection of the PMMA. Kyphoplasty results in an increase in vertebral height, which may provide a biomechanical advantage. Although this technique is growing in popularity, outcomes in the published literature regarding treatment of metastatic disease are still minimal. Fourney et al.¹⁰⁵ described a case series of 97 procedures in 56 patients. A total of 84% of patients had marked or complete pain relief. These results appear to be comparable to the larger volume of literature on kyphoplasty as a treatment of osteoporosis-related vertebral fractures.¹⁰⁶

Management of Bone Pain From Cancer

Key Points:

- The goal of therapy is to enhance patient comfort and quality of life; combinations of pharmacologic and nonpharmacologic strategies may be required.
- Radiopharmaceuticals are an underused form of management of cancer-related bone pain.
- A major unanswered issue is whether marrow-toxic chemotherapy can be given safely concurrently with radiopharmaceuticals.

Treatment objectives of pain management of bone metastases are straightforward; palliate pain, improve quality of life, prolong pain-free survival, and eradicate tumor cells in the bone. Treatment can be broadly divided into analgesic therapy, other pharmacothera-

peutic approaches, and nonpharmacotherapeutic approaches. Pharmacotherapeutic approaches include chemotherapy, hormone therapy, bisphosphonates, steroids, and radiopharmaceuticals. Nonpharmacotherapeutic approaches include external beam radiation therapy, orthopedic intervention, nerve blocks, and kyphoplasty and RFA.

Radiopharmaceutical Management

Three radiopharmaceuticals have been approved by the FDA: samarium-153 lexitronam intravenous injection (samarium), strontium-89 chloride intravenous injection (strontium), and phosphorus-32 (phosphorus), administered either intravenously or orally. Phosphorus is not commonly used because of toxicity to the bone marrow. Both samarium and strontium are administered as single intravenous injections. Strontium is associated with skeletal uptake in primary bone tumors and areas of metastatic involvement. Repeat doses are not recommended at intervals less than 90 days. In a study of 118 patients with metastatic bone pain receiving strontium-89, Kaslicky et al.¹⁰⁷ reported that the mean painless period after one dose was 3.3 months. Patients without myelosuppression who experienced response were treated up to 5 times over 3 years.

Some physicians prefer samarium over strontium because the dose of samarium can be tailored to the patient's body weight, whereas strontium is administered as a fixed dose. In addition, samarium is less myelosuppressive and can be given at about 6-week intervals. Samarium can also be imaged to define the targeting of metastatic osseous lesions. Serafini et al.¹⁰⁸ reported the results of a study that randomized 118 patients with metastatic bone pain to receive 1 of 2 different doses of samarium or placebo. Based on both physician and patient assessment, 62% to 72% of treated patients experienced pain relief, with a 31% incidence of marked or complete relief, beginning as early as week one. Bone marrow toxicity was mild and reversible. In a placebo-controlled randomized study of 152 patients with hormone refractory prostate cancer and metastatic bone pain, Sartor et al.¹⁰⁹ found significant improvement in pain, based on patient assessment, in the samarium treatment group. Pain relief occurred rapidly, with significant improvement within the first 2 weeks after injection, leading to significant decreases in opioid use by week 3.

Currently, radiopharmaceuticals are indicated for the palliative treatment of pain only, although some

data suggest an anti-tumor effect as well. However, many physicians may not consider radiopharmaceuticals until multiple other treatment regimens have failed. At this point, patients may have developed low bone marrow reserve, limiting the use of radiopharmaceuticals. Alternatively, physicians may be hesitant to give a marrow-toxic agent for pain relief only, because it might preclude later therapeutic drugs. A major unanswered issue is whether marrow-toxic chemotherapy can be given safely concurrently with radiopharmaceuticals.

Conclusions

Bone health has become an important consideration for patients with primary and metastatic cancers. An understanding of the pathophysiology of normal bone remodeling, pathophysiology of bone metastases, and appropriate evaluation for bone health is important for the optimal management of patients with cancer. Appropriate imaging for BMD can be accomplished with DXA scanning. Bone biomarkers can be used to complement the measurements of BMD and may be important for assessing efficacy of antiresorptive therapy in osteopenia, osteoporosis, and bone metastases. Antiresorptive therapy, bisphosphonates in particular, has a broad range of applications, including treating osteopenia and osteoporosis, preventing bone loss, and managing bone metastases. Surgical management of bone metastases is best done by a team with surgical oncologic expertise and careful evaluation of the patient. Further evaluation of radiopharmaceutical therapy is warranted in metastatic disease. Bone health and maintenance of bone integrity is an important component of cancer care in both early and late stage of disease.

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Post-test

Please circle the correct answer on the enclosed answer sheet.

1. Which of the following are risk factors for bone loss commonly seen in oncology patients?
 - a. Aromatase inhibitor therapy
 - b. Hypogonadism
 - c. Chemotherapy-induced premature menopause
 - d. Glucocorticoid therapy
 - e. All of the above
 - f. None of the above
2. Which of the following statements is TRUE regarding DXA imaging?
 - a. DXA machines are standardized such that the results are consistent between machines.
 - b. For serial monitoring of bone loss, it is important to use the same DXA machine at the same anatomic site.
 - c. The Z score is the most useful measure in assessing fracture risk.
 - d. Serial DXA scans should never be done at intervals shorter than 2 years.
3. Which of the following statements is FALSE regarding bone biomarkers?
 - a. Changes in bone turnover markers can reflect response to antiresorptive therapy in weeks rather than months to years needed by DXA.
 - b. The clinical use of bone turnover markers has focused on monitoring response and effectiveness of antiresorptive therapies.
 - c. Bone turnover markers can be used to assess therapy compliance.
 - d. Bone turnover markers show little variation with underlying physiology and thus can be measured at any point in the day.
4. Which of the following statements is/are TRUE regarding antiresorptive agents?
 - a. There is a close correlation between the increase in BMD and the decreased risk of fracture.
 - b. Randomized trials of cancer patients have consistently shown that antiresorptive agents decrease fracture risk.
 - c. Testosterone improves both bone mass and body composition and has been shown to decrease fracture risk.
 - d. b,c above
 - e. All of the above
 - f. None of the above
5. Which of the following is/are TRUE regarding emerging therapies for preventing bone loss?
 - a. Osteoprotegerin (OPG) analogues function by blocking RANK-L, an essential cytokine that controls the development of osteoclasts from precursor macrophage/monocyte cells.
 - b. Denosumab is a human monoclonal antibody to RANK-L; studies have shown that denosumab can increase the bone mineral density in postmenopausal women.
 - c. TGF-beta is a cytokine that is released by osteoclasts and also secreted by tumor cells, creating a vicious cycle of bone resorption; TGF-beta may emerge as a therapeutic target.
 - d. Bone resorption is primarily related to circulating hormones and cytokines, and unrelated to the bone microenvironment.
 - e. a,b,c above
 - f. All of the above
6. Which of the following is FALSE regarding chemotherapy-induced ovarian failure?
 - a. Chemotherapy-induced ovarian failure occurs in 50% to 70% of pre- and perimenopausal women with breast cancer treated with chemotherapy.
 - b. A lower baseline BMD increases the risk of ovarian failure.
 - c. A variable definition of chemotherapy-induced ovarian failure makes it difficult to study this issue.
 - d. Aromatase inhibitors are only appropriate for postmenopausal women; thus the definition of menopause has important clinical implications.
7. Which of the following is/are TRUE regarding the skeletal complications of prostate cancer?
 - a. The incidence of fracture is higher in men receiving androgen deprivation therapy compared to those without.
 - b. Hypogonadism results in a pattern of very gradual bone loss only detectable after several years.
 - c. Selective estrogen receptor modulators may also have a role in prostate cancer; a randomized trial of raloxifene has shown significant increases in the BMD of the hip.
 - d. a,c above
 - e. All of the above
 - f. None of the above
8. Which of the following is FALSE?
 - a. Most metastases from prostate cancer contain both osteoblastic and osteolytic components.
 - b. Osteolysis is characterized by high levels of urinary NTx, which are in turn a risk factor for skeletal related events.
 - c. Treatment and disease related bone loss provides the rationale for bisphosphonate therapy in patients with bone metastases from prostate cancer.
 - d. A large randomized trial failed to show any effect of zoledronic acid in reducing the incidence of skeletal related events compared to placebo.
9. Which of the following is/are TRUE regarding the pathophysiology of bone metastases?
 - a. Bone metastases are typically either purely osteolytic or osteoblastic.
 - b. Osteolytic and osteoblastic metastases have distinct pathways at the cellular level.
 - c. The bone matrix is largely inert.
 - d. Tumor cells can produce many factors that stimulate osteoblasts.
 - e. All of the above
 - f. None of the above

10. Which of the following is/are FALSE regarding imaging of bone metastases?
- a. Given the multiple imaging options, including plain radiography, skeletal scintigraphy, CT scan, MRI, PET, PET/CT fusion studies, and multiplanar SPECT/CT, it is relatively straightforward to distinguish a benign from malignant process.
 - b. The inability to accurately follow bone lesions is one reason that patients with bone metastases are generally excluded from clinical trials unless they have measurable disease in other locations.
 - c. Skeletal scintigraphy has largely been replaced by PET/CT fusion as the initial imaging modality to assess bone metastases.
 - d. Interpretation of imaging modalities for bone metastases requires simultaneous review of all relevant imaging studies with full clinical context.
 - e. a,b,c above
 - f. a,c above
11. Which of the following is/are TRUE regarding surgical management of bone metastases?
- a. Surgical principles of traumatic fracture management cannot be extrapolated to management of pathologic fracture.
 - b. Surgical management is focused on providing stabilization but rarely can relieve pain.
 - c. A variety of minimally invasive techniques is also available, including radiofrequency ablation (RFA) and percutaneous osteoplasty, also referred to as cementoplasty.
 - d. a,c above
 - e. All of the above
 - f. None of the above
12. Which of the following is/are TRUE regarding radiopharmaceutical treatment of bone pain?
- a. The 3 FDA-approved radiopharmaceuticals for bone pain are samarium-153 lexidronam IV, strontium-89 chloride IV, and phosphorus-32, either IV or oral.
 - b. Some physicians prefer samarium over strontium, since samarium is less toxic to the bone marrow and dose can be tailored to the patient's body weight.
 - c. Radiopharmaceuticals are an underused form of management of cancer-related bone pain, not considered until other treatment regimens have failed.
 - d. When used late in the course of disease, low bone marrow reserve may limit their use.
 - e. All of the above
 - f. None of the above

Post-Test Answer Sheet													
Please circle one answer per question. A score of at least 70% on the post-test is required.													
1.	a	b	c	d	e	f	7.	a	b	c	d	e	f
2.	a	b	c	d			8.	a	b	c	d		
3.	a	b	c	d			9.	a	b	c	d	e	f
4.	a	b	c	d	e	f	10.	a	b	c	d	e	f
5.	a	b	c	d	e	f	11.	a	b	c	d	e	f
6.	a	b	c	d			12.	a	b	c	d	e	f

<p>Please evaluate the achievement of the educational objectives using a scale of 1 to 5.</p> <p>(1 = Not met; 3 = Partially met; 5 = Completely met)</p> <p>Understand screening and detection of osteoporosis 1 2 3 4 5</p> <p>Define biomarkers in bone health 1 2 3 4 5</p> <p>Identify treatment options for osteoporosis 1 2 3 4 5</p> <p>Recognize chemotherapy-induced ovarian failure 1 2 3 4 5</p> <p>Understand chemotherapy-induced bone loss 1 2 3 4 5</p> <p>Understand management of skeletal complications of breast and prostate cancer 1 2 3 4 5</p> <p>Understand pathophysiology and imaging of bone metastases 1 2 3 4 5</p> <p>Define surgical management of bone metastases 1 2 3 4 5</p> <p>Understand management of bone pain related to metastases 1 2 3 4 5</p>	<p>Please indicate the extent to which you agree or disagree with the following statements:</p> <p>(1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)</p> <p>The material was presented in a fair and balanced manner. 1 2 3 4 5</p> <p>The information presented in this monograph was pertinent to my educational needs. 1 2 3 4 5</p> <p>The information presented was scientifically rigorous and up-to-date. 1 2 3 4 5</p> <p>The information presented in this monograph has motivated me to modify my practice. 1 2 3 4 5</p> <p>I would recommend this monograph to my colleagues. 1 2 3 4 5</p>
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**NCCN Task Force Report: Bone Health
and Cancer Care**

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