NCCN Task Force Report:
Bone Health in Cancer Care

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Target Audience
This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with cancer.

Learning Objectives
Upon completion of this activity, participants should be able to:
• Describe imaging techniques for screening and detection of bone loss in patients with cancer and surgical management of bone metastasis
• Identify the appropriate management strategy for treatment-induced bone loss and skeletal complications associated with breast and prostate cancers
• Discuss the safety concerns of bone modifying agents and guidelines related to management of associated toxicities
• Communicate with the patient the rationale for bone-modifying agent
• Establish goals of bone-modifying therapy with the patient

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Abstract

Bone health and maintenance of bone integrity are important components of comprehensive cancer care. Many patients with cancer are at risk for therapy-induced bone loss, with resultant osteoporotic fractures, or skeletal metastases, which may result in pathologic fractures, hypercalcemia, bone pain, and decline in motility and performance status. Effective screening and timely interventions are essential for reducing bone-related morbidity. Management of long-term bone health requires a broad knowledge base. A multidisciplinary health care team may be needed for optimal assessment and treatment of bone-related issues in patients with cancer. Since publication of the previous NCCN Task Force Report: Bone Health in Cancer Care in 2009, new data have emerged on bone health and treatment, prompting NCCN to convene this multidisciplinary task force to discuss the progress made in optimizing bone health in patients with cancer. In December 2012, the panel members provided didactic presentations on various topics, integrating expert judgment with a review of the key literature. This report summarizes issues surrounding bone health in cancer care presented and discussed during this NCCN Bone Health in Cancer Care Task Force meeting. (JNCCN 2013;11[Suppl 3]:S1–S50)

Assessing Bone Health

Osteoporosis and its associated increase in fracture risk is a major health issue for the aging population, and especially for patients with cancer. Hip and vertebral fractures are associated with chronic pain, decreased quality of life, and increased risk of death.¹ Much of the morbidity and mortality associated with bone loss can be prevented with appropriate screening, lifestyle interventions, and therapy.

Both cancer itself and cancer therapies can have profound effects on bone metabolism. The hormone deprivation state resulting from certain cancer therapies enhances osteoclastic bone resorption, promoting bone loss. Osteoporosis risk factors unique to patients with cancer include chemotherapy-induced menopause, gonadotropin-releasing hormone (GnRH) suppression of gonadal function, antiestrogen and antiandrogen therapies, and glucocorticoids used predominantly in treatment of hematologic malignancies or as supportive agents in solid tumors. 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.

These cancer therapy-related affects combine with other important clinical factors, such as age, prior fracture history, and family history of fracture, to further increase fracture risk.²³ Lifestyle-related factors, such as smoking, excess alcohol intake, inadequate weight-bearing exercise, low calcium intake, and vitamin D deficiency, are common in patients with cancer. Additionally, the use of specific nononcologic pharmacologic agents, such as proton pump inhibitors, anticoagulants, and certain antidepressants, may contribute to accelerated bone loss in these patients. Breast cancer in particular is associated with increased rates of osteoporosis and fractures, as shown in several studies. Researchers found a 2.72% annual incidence of vertebral fractures in 352 patients with newly diagnosed breast cancer, compared with 0.53% in a control group of 776 women.⁴ In a study by the Women’s Health Initiative (WHI) group, postmenopausal breast cancer survivors had a significantly higher incidence of total fractures.⁵
Bone Mineral Density

The WHO established fracture risk through comparing the bone mineral density (BMD) of an individual versus the database measurements of normal men or women of specific ethnic backgrounds in whom fracture frequency has been ascertained. A variety of different technologies are available for assessing BMD, including dual-energy x-ray absorptiometry (DXA), peripheral ultrasound, and quantitative CT scanning. However, DXA of the hip and spine is considered the gold standard because of its intermediate cost, low radiation exposure, excellent precision, ability to monitor treatment response, and validation in a large number of clinical trials.

BMD may be expressed in absolute terms, in grams per square centimeter (g/cm²), and in relative terms as the difference in standard deviations from expected BMD for the patient’s age and sex (Z score) or from that of “young normal” adults of the same sex (T score). In 1994, the WHO established diagnostic criteria for osteoporosis based on T scores. Based on the WHO criteria, BMD within 1.0 standard deviation of a “young normal” adult (T score of ≥ –1.0) is considered normal; 1.0 and 2.5 standard deviations below (T score of –1.0 to –2.5) constitutes low bone mass; and 2.5 standard deviations or more below (T score ≤ –2.5) constitutes osteoporosis. Evidence shows that low BMD measured with DXA at any skeletal site (spine, hip, or forearm) can predict osteoporotic fracture; the BMD value at a given site best predicts fracture risk at that specific site. Overall, an approximately 2-fold increase in risk of these fractures exists for each standard deviation decrease in BMD.

The limitations of DXA measurement must also be recognized. For example, results can vary with the machine used, the different underlying dual-energy methods used, calibration differences, different detectors used, different reference standards, and also by anatomic site (e.g., hip vs vertebral). Therefore, serial monitoring of BMD, using the same piece of equipment and the same reference standards, is recommended. The presence of osteoarthritis or calcification of the aorta may lead to falsely high BMD. A T score of –2.5 should not be interpreted as the definitive cutoff 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, a condition characterized by inadequate mineralization of bone caused by vitamin D deficiency or hypophosphatemia. A DXA scan exposes patients to low levels of radiation, equal to approximately one-tenth of those from a chest radiograph, and equivalent to daily background radiation exposure.

The U.S. Preventive Services Task Force recommends screening for osteoporosis in all women older than 65 years without previous known fractures or secondary causes of osteoporosis, and in women younger than 65 years whose 10-year fracture risk is equal to or greater than that of a 65-year-old white woman without additional risk factors. It does not recommend screening in men with no history of fractures or known secondary causes of osteoporosis. ASCO guidelines are in agreement, and further suggest BMD screening for women with breast cancer who have high-risk factors, such as those with a family history of fractures, body weight less than 70 kg, and prior nontraumatic fracture, and those of any age who are postmenopausal receiving aromatase inhibitor (AI) therapy, and those who are premenopausal with therapy-induced ovarian failure. The National Osteoporosis Foundation (NOF) recommends BMD testing in the following individuals: women aged 65 years and older and men aged 70 years and older, regardless of clinical risk factors; younger postmenopausal women in the menopausal transition, and men aged 50 to 69 years with clinical risk factors for fracture; adults who have a fracture after age 50 years; and all adults with a condition (eg, rheumatoid arthritis) or taking a medication (eg, glucocorticoids in a daily dose of ≥5 mg of prednisone or the equivalent for ≥3 months) associated with low bone mass or bone loss.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer recommend screening for osteoporosis according to guidelines for the general population from the NOF (www.nof.org). In patients who will be undergoing therapy that lowers sex steroids, the NCCN Guidelines for Breast and Prostate Cancers recommend evaluation with baseline and periodic follow-up DXA scans to evaluate bone health and risk of fracture (to view the most recent version of these guidelines, visit NCCN.org). Fracture Risk

The WHO developed the Fracture Risk Assessment tool (FRAX), a risk-assessment software that combines both bone density measurements and clinical factors in assessing fracture risk (www.shef.ac.uk/FRAX/).
This tool provides an estimate of the 10-year probability of hip fracture and a major osteoporotic fracture based on age, sex, clinical risk factors, femoral neck BMD (T score), and other information. FRAX analysis is optimized for postmenopausal women and men aged 50 years and older, and is intended to predict risk for patients previously untreated for bone loss. The WHO FRAX tool can be used to guide intervention and therapy. Guidelines promulgated by the Agency for Healthcare Research and Quality recommend therapeutic intervention for patients with a 10-year FRAX risk of 3% or greater for hip fractures and 20% or greater for all major fractures. FRAX is not designed to evaluate fracture risk in patients undergoing osteoporosis therapy. Cancer therapy, including AIs and androgen deprivation therapy (ADT), should be considered “secondary osteoporosis” while using the FRAX algorithm; glucocorticoid use (eg, use of ≥5 mg/d of prednisone or an equivalent for ≥3 months) should be indicated by checking the box entitled “glucocorticoids.” FRAX calculations can be performed with or without BMD data, making it useful when bone density information is unavailable.

**Bone Turnover Markers**

Biochemical markers of bone remodeling can be broadly subdivided into markers of bone formation (bone-specific alkaline phosphatase [BAP], and N-terminal and C-terminal pro-peptides of type I procollagen [P1NP, P1CP]) and markers of bone resorption (N-terminal and C-terminal cross-linking telopeptides of type I collagen [NTX and CTX]). Bone biomarkers can be used to assess risk of fracture independently of age, BMD, and prior fracture. Several cohort studies have shown that levels of bone markers such as CTX and BAP are predictive of vertebral fractures and hip fractures, and bone turnover markers may improve the identification of women at high risk for fracture. However, the markers of bone metabolism cannot be translated into a patient-specific estimate of risk for fracture; hence, the bone markers are not widely used clinically when addressing osteoporosis.

**Vertebral Fractures**

Vertebral fractures, the most common type of fragility fractures, are associated with a significant increase in morbidity and mortality, and may predict risk of future fracture. These can occur with no recognizable trauma, and may not cause pain sufficient to arouse concern. Clinical indications of vertebral fractures include a historical height loss of greater than 4 cm (1.6 in) or a prospective height loss of greater than 2 cm (0.8 in), or complaint of acute back pain. Many patients with vertebral fractures may not have T scores classified as osteoporosis. Independent of BMD and other clinical risk factors, existing vertebral fractures are a strong predictor of future fractures. Women with vertebral fractures have a 5-fold increased risk of a new vertebral fracture and a 2-fold increased risk of hip fracture.

Vertebral fracture assessment (VFA) can be performed along with BMD assessment by DXA. It is available as additional software on some bone densitometers. The software permits lateral vertebral assessment and provides crisp lateral images of the thoracic and lumbar spine with relatively low radiation exposure. Other methods to detect and evaluate vertebral fractures include spine radiography and CT. Lateral spine radiographs are the gold standard for detecting vertebral fractures; they expose patients to a relatively higher dose of radiation than VFA, which uses a relatively low dose of radiation. The approximate effective radiation dose of VFA is 3.00 μSv versus 1.5 mSv with radiograph of lumbar spine, 0.001 mSv with DXA, 0.10 mSv for chest radiograph, and 6.00 mSv with CT scan of the spine.

**NCCN Recommendations for Screening for Osteoporosis in Patients With Cancer**

According to the NCCN Task Force, patients with cancer typically have several additional osteoporosis risk factors that should prompt screening, regardless of age or sex. The task force recommends screening all patients with cancer who are at increased risk for bone loss because of therapy and/or age. All patients who initiate cancer therapy that induces early menopause, reduces sex steroids or interferes with their action, or includes glucocorticoids should undergo assessment of their risk for bone loss and subsequent risk for osteoporosis and fracture. Obtaining a bone-related history and physical examination, including the use of the FRAX calculator, is recommended to estimate fracture risk.

Changes in DXA scan in response to antiresorptive medication typically occur over a long period, and serial DXA scans should generally not be performed more than once a year. The task force rec-
ommends that patients with cancer with elevated fracture risk should be evaluated with DXA every 24 months. In selected circumstances, such as when bone loss risks have changed significantly or a major therapeutic intervention has been undertaken, obtaining a 12-month follow-up DXA is reasonable.

Baseline and follow-up history and physical examinations should include assessment for vertebral fractures, including obtaining a history of falls, annual height measurement, and evaluation of new back pain. Vertebral fracture assessment may be helpful in the baseline assessment and follow-up of patients with a very high risk of vertebral fracture.

Patients with clinical evidence of an existing vertebral fracture should be carefully assessed for all factors affecting future fracture risk, and risk intervention strategies, including possible therapeutic intervention, should be undertaken. Figure 1 presents an algorithm for the screening of patients with cancer at increased risk for bone loss and/or fracture as a result of their cancer therapy or age.

**Cancer Therapy and Bone Health**

Many of the therapies used for the treatment of breast and prostate carcinomas are associated with bone density loss, which in turn leads to an increased risk of fracture. Rates of bone density loss can vary significantly across subgroups of patients. For example, bone loss is more significant in premenopausal women with treatment-induced ovarian suppression combined with an AI compared with postmenopausal women treated with an AI. The magnitude of effects of various cancer treatments on BMD is illustrated in Figure 2.

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**Figure 1** Algorithm for the management of bone health in cancer patients in the United States.

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, Fracture Risk Assessment tool.
Chemotherapy-Induced Ovarian Failure and Bone Health

Nearly all premenopausal women with breast cancer receiving standard adjuvant chemotherapy experience at least temporary amenorrhea, and as many as 50% to 70% may experience permanent ovarian failure or early menopause.30,31

No standard definition for chemotherapy-induced ovarian failure exists in the literature. For example, some studies define chemotherapy-induced ovarian failure as at least 3 or 6 months of amenorrhea. However, distinguishing between temporary amenorrhea that will reverse and permanent ovarian failure is important, because bone loss is of greatest magnitude in the group of patients that goes into permanent ovarian failure.32,33

The effects of chemotherapy on ovarian function depend on age at treatment, the specific class of drugs, and the cumulative doses. An important factor for predicting the risk of premature menopause or ovarian failure is age at chemotherapy treatment, because greater risk is seen with increasing age.31,33 Chemotherapy with alkylating agents such as cyclophosphamide is associated with highest risk of ovarian failure, followed by therapy with platinum agent and anthracyclines. Additional risk factors include cumulative dose and/or duration of the chemotherapy.31,34 Data from small studies have suggested other risk factors for developing ovarian failure, such as a higher baseline BMD before initiating adjuvant chemotherapy.35

Chemotherapy-induced ovarian failure is a high-risk factor for bone loss, which occurs as early as 6 months and increases further at 12 months.35,36 Several studies have reported accelerated bone loss as a consequence of ovarian failure after adjuvant chemotherapy.35,37–41 In a prospective study of 49 premenopausal women (median age, 42 years) with breast cancer receiving adjuvant chemotherapy, 35 women experienced chemotherapy-induced ovarian failure.35 In patients with ovarian failure, significant bone loss was seen in the lumbar spine by 6 months, but no significant bone loss was seen in the normal men.
change was seen in patients who retained ovarian function. Bone loss associated with chemotherapy-induced menopause is several-fold higher than that seen with natural menopause or AI therapy–induced bone loss in postmenopausal women.\textsuperscript{35,42–44}

**Hormonal Therapy and Bone Health**

**Aromatase Therapy and Bone Loss:** AIs play an important role in the treatment of postmenopausal women with estrogen or progesterone receptor–positive breast carcinoma, both in the adjuvant and metastatic settings.\textsuperscript{12}

AIs cause a rapid decline of circulating estrogen levels—as much as 99% within as little as 6 weeks.\textsuperscript{45,46} The AI-induced estrogen depletion far exceeds the gradual estrogen loss seen in healthy menopausal women.\textsuperscript{47} Therefore, in these postmenopausal women, natural bone loss is accelerated by the further reduction in circulating estrogen caused by AIs.\textsuperscript{48,49}

The rate and magnitude of bone loss caused by AIs are lower than those observed after ovarian suppression or chemotherapy-induced ovarian failure (Figure 2). Major phase III trials involving AIs in the adjuvant setting have reported increased fracture risk.\textsuperscript{50–53} Therefore, AI use is considered a high-risk factor for osteoporosis.

In the ATAC trial, after a median follow-up of 100 months, patients receiving anastrozole alone had a significantly higher fracture incidence compared with those receiving tamoxifen alone (2.93% for anastrozole vs 1.90% for tamoxifen; \(P<.0001\)).\textsuperscript{54} However, the pronounced difference in annual fracture incidence rates observed during therapy did not persist beyond the 5-year treatment period (1.56% vs 1.51%, respectively, at 100 months; \(P=.79\)), suggesting that AI-related fracture rates decrease after treatment completion.\textsuperscript{52} In a recent longer-term follow-up analysis of the ATAC bone substudy in a small group of 50 patients, evidence showed partial recovery in BMD at the lumbar spine (7 years after therapy) and no further loss in BMD at the hip in the anastrozole group.\textsuperscript{54} Patients with a normal BMD or who were osteopenic after 5 years of anastrozole treatment did not become osteoporotic at the end of 7 years after treatment.\textsuperscript{54}

In the ARNO/ABCSG8 trial, fracture rates significantly increased in patients who switched to anastrozole after 2 years on tamoxifen compared with those who received continuous therapy with tamoxifen for 5 years (anastrozole, 2% vs tamoxifen, 1%).\textsuperscript{53} However, the fracture rate in the anastrozole group in ARNO/ABCSSG8 was lower than that seen at a similar point in the anastrozole group of the ATAC trial.\textsuperscript{52} The Breast International Group (BIG) 1-98 trial compared adjuvant tamoxifen with adjuvant letrozole. Similar to the ATAC trial, results of the BIG 1-98 trial show increased incidence of bone fracture in patients treated with letrozole compared with tamoxifen (5.7% vs 4.0%; \(P<.001\)).\textsuperscript{55} Analysis after 5 years of treatment showed that women receiving letrozole continued to have significantly more fractures than those receiving tamoxifen (8.6% vs 5.8%; \(P<.001\)).\textsuperscript{50}

The Intergroup Exemestane Study compared adjuvant tamoxifen for 5 years with 2 to 3 years of tamoxifen followed by exemestane.\textsuperscript{51} The incidence of fracture at 58 months was significantly higher in the exemestane group than in the tamoxifen group (7.0% vs 4.9%; \(P=.003\)).\textsuperscript{56}

The MA-17 trial compared an additional 5 years of letrozole versus placebo after an initial 5 years of adjuvant tamoxifen.\textsuperscript{57} The design of this trial allowed for a more direct look at the effect of AIs on bone without the confounding factor of tamoxifen present in the comparator arm. The incidence of a new diagnosis of osteoporosis was slightly higher in the letrozole group than in the placebo group (5.8% vs 4.5%; \(P=.07\)), with similar fracture rates in the 2 groups. Regular treatment with calcium and vitamin D and the bone protective effect of pretreatment with tamoxifen probably contributed to this result.

The MA-27 trial randomized postmenopausal patients with breast cancer to either adjuvant exemestane or anastrozole.\textsuperscript{58} A substudy of BMD changes was performed to clarify whether the androgenic nature of exemestane results in less effect on bone density compared with a nonsteroidal AI. Data in approximately 500 women showed that among patients without osteoporosis, less early bone loss occurred at the hip in the exemestane group compared with the anastrozole group (1 year; \(P=.007\); however, at 2 years, the difference was no longer significant (\(P=.13\)). For women with osteoporosis, bisphosphonate, calcium, and vitamin D increased BMD despite AI therapy at 1 and 2 years.\textsuperscript{59} Clinical bone fractures on study were reported to be similar between the groups.\textsuperscript{59}

**ADT and Bone Loss:** Prostate cancer growth is driven by androgen hormones, and therefore ADT, either by orchectomy or administration of GnRH agonists,
is the backbone of systemic therapy for prostate cancer. Based on a study in the US Medicare population, the use of ADT increased from 1.8% in 1993 to 2.9% in 2000. A study of men with newly diagnosed prostate cancer from the CaPSURE database recorded that 46% of men (679 of 1485) with prostate cancer received ADT.60 Long-term ADT is used for treating locally advanced, recurrent, and metastatic prostate cancer.19 Osteoporosis and greater fracture risk have emerged as important long-term adverse effects of ADT. A recent survey of 175 patients revealed that most men undergoing ADT do not receive appropriate screening, lack basic information, and are not actively engaged in managing bone health to prevent and manage loss.61

The term ADT is used because its intended therapeutic use is to lower testosterone levels. Because estradiol is produced from testosterone through aromatase activity, ADT also reduces estradiol levels.62,63 Compelling data suggest that estradiol has important effects in men.64 In population-based studies of older men, low estradiol levels are associated with low bone mass and greater fracture incidence than low testosterone levels.65

ADT using either orchidectomy or GnRH agonists or antagonists with or without antiandrogens has been shown to decrease BMD in patients with prostate cancer.66–70 The decrease in BMD is most dramatic in the first year after ADT initiation, and is approximately 2% to 5%.71 In comparison, the age-related decline in men is 0.5% to 1.0% per year.66,68,72–75 Additionally, further loss occurs with continued treatment.76 Consequently, the development of osteoporosis and fracture risk seems to increase steadily with duration of ADT. In large population-based studies, for example, ADT was associated with a 21% to 54% relative increase in fracture risk.74,77,78 A study of records from SEER and Medicare databases of more than 50,000 men with prostate cancer revealed that the frequency of any fracture was significantly higher in those receiving ADT.77 The relative risk of the occurrence of any fracture or a fracture resulting in hospitalization increased with the increasing number of doses of GnRH agonist received during the first year after diagnosis. A Medicare claims–based study characterized the relationship between GnRH agonists and risk for clinical fractures.74 Men with nonmetastatic prostate cancer (n=10,617) were matched for age, race, geographic location, and comorbidity. Of these, 3887 men treated with GnRH agonist were compared with 7774 patients not treated with GnRH agonists.74 GnRH agonist use was associated with a faster time to fracture and a significantly increased risk for any clinical fracture, hip/femur fractures, and vertebral fractures. Short-term treatment did not confer any greater fracture risk, suggesting reversal of the hypogonadal effects on the bone.

Management of Bone Health in Patients With Cancer

Initial strategies for preventing bone loss and osteoporosis include nonpharmacologic recommendations for lifestyle and nutritional modifications, including performing regular weight-bearing exercises and physical activity, avoiding tobacco use, limiting alcohol intake, and having adequate intake of calcium and vitamin D. In addition to lifestyle and nutritional interventions, pharmacologic options should be considered in patients at high risk for bone loss and/or fracture.

Nonpharmacologic Components

Lifestyle Modifications: An excellent patient resource for bone health and lifestyle behavior is the NOF Web site.79 Physical activity can improve muscle mass, muscle strength, balance, and bone strength. Weight-bearing exercise has been associated with a decreased risk of hip fractures. This is likely through a reduction in fall risk and modest effects on preservation of bone density.80–82 Walking, Tai Chi, physical therapy, and dancing are considered good options to improve balance and prevent falls. Adults should aim for at least 30 minutes per day of moderate physical activity (either in one continuous session or in many shorter bursts). A home safety checklist can be found on the NOF Web site (www.nof.org).79 Wearing hip protectors may prevent hip fracture in the event of a fall83–86 and may be considered for patients with an exceptionally high risk for falling. However, the use of hip protectors has had limited success in randomized controlled trials because of lack of adherence.87 Toxic lifestyle behaviors, such as tobacco abuse and excessive alcohol consumption, are associated with a variety of adverse health outcomes, including increased risk for osteoporosis and fracture. Counseling patients on these topics is important on many levels and should not be overlooked.
The interventions chosen to follow will vary on an individualized basis (eg, referral to a smoking cessation clinic).

**Calcium and Vitamin D Supplementation:** Adequate intake of calcium and vitamin D is critical to bone health and prevents secondary hyperparathyroidism. Some randomized studies have shown that calcium and vitamin D supplementation decreases the risk of fractures.\(^8\)\(^8\)\(^-\)\(^9\)\(^0\) Many of the negative studies have been hampered by poor compliance with supplements and/or suboptimal doses of vitamin D.

**Calcium Supplementation:** The updated Institute of Medicine (IOM) recommendations are 1200 mg/d of calcium for women and 1000 mg/d for men between 51 and 70 years, and 1200 mg for all individuals older than 70 years, with an upper level intake of 2000 mg/d.\(^9\)\(^1\) For individuals older than 50 years, the NOF recommends at least 1200 mg/d of calcium (from food and supplements).\(^7\)\(^9\)

Calcium supplements are available as calcium carbonate or calcium citrate. Calcium carbonate requires gastric acid for optimal absorption and should therefore be taken with food. Calcium citrate does not require gastric acid for absorption, can be taken in between meals, and is the preferred option in patients receiving proton pump inhibitors. For optimal absorption, calcium supplements should be taken in divided doses of no more than 600 mg at one time. The upper limit of calcium set by the IOM is 2500 mg/d for all adults aged 19 to 50 years and 2000 mg/d for adults older than 50 years.\(^9\)\(^1\) Evidence from the WHI study shows that adding 500 mg twice daily of calcium supplements to women with a baseline mean calcium intake of 1100 to 1200 mg/d increases the risk of developing kidney stones. Whether calcium supplements raise the risk of cardiovascular disease, as has been shown in some meta-analyses, is currently debated.\(^9\)\(^2\)\(^-\)\(^9\)\(^4\) For patients at risk for nephrolithiasis, increasing dietary calcium in food has been associated with a lower risk for nephrolithiasis compared with calcium supplements.\(^9\)\(^2\)

**Vitamin D Supplementation:** Vitamin D is known to play a major role in gastrointestinal calcium absorption and is essential for maintaining normal bone mineralization. Vitamin D is produced endogenously when ultraviolet rays strike the skin. Use of sun block, recommended to reduce the risk of skin cancer, leads to substantial reduction of cutaneous vitamin D synthesis. Vitamin D is naturally present in very few foods, but is added as a supplement to some food products and is available as a dietary supplement. Vitamin D supplementation is reported to increase BMD\(^9\)\(^5\) and reduce the risk of falls (possibly through impacting muscle function and/or balance).\(^8\)\(^2\)\(^,\)\(^9\)\(^0\)\(^,\)\(^9\)\(^6\)

The NOF recommends that healthy people aged 19 to 49 years get 400 to 800 IU of vitamin D every day; and that adults aged 50 years and older get 800 to 1000 IU every day. In the updated recommendations regarding vitamin D intake,\(^9\)\(^7\) the IOM recommends 600 IU of vitamin D every day for most healthy adults younger than 71 years and 800 IU for healthy people aged 71 years and older. This is an increase from the previous IOM recommendations. Although the updated IOM recommendations for vitamin D intake are sufficient for most healthy adults, they do not address the vitamin D requirements for individuals at high risk for bone loss and/or osteoporosis.

Vitamin D deficiency or insufficiency is common in the general population and in patients with cancer.\(^9\)\(^8\)\(^-\)\(^1\)\(^0\) Although vitamin D is clearly important for bone health, evidence for its role in multiple other health outcomes remains uncertain. The Endocrine Society Guidelines recommend using the serum circulating 25(OH) D level, measured with a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency.\(^1\)\(^0\)\(^1\) Vitamin D deficiency is defined as a 25(OH) D level below 20 ng/mL (50 nmol/L), and vitamin D insufficiency as a 25(OH) D level of 21 to 29 ng/mL (525–725 nmol/L).

Vitamin D supplements are available in 2 forms: D\(_2\) (ergocalciferol) and D\(_3\) (cholecalciferol). These forms are metabolized differently, and vitamin D\(_3\) could be more effective in raising 25(OH) D concentrations and maintaining those levels when higher doses and longer dosing intervals are used.\(^1\)\(^0\)\(^2\)\(^,\)\(^1\)\(^0\)\(^3\) When daily dosing was studied, no difference was found in maintaining 25(OH) D levels.\(^1\)\(^0\)\(^4\)

For optimal bone health, vitamin D should be supplemented in amounts sufficient to bring the serum 25(OH) D level to 30 ng/mL (75 nmol/L) or higher.\(^1\)\(^0\)\(^1\) A higher dose repletion regimen followed by a lower dose maintenance regimen is required. One common treatment regimen for patients with serum 25(OH) D levels below 30 ng/mL is prescription vitamin D\(_2\) (ergocalciferol) 50,000 IU (available only by prescription) weekly for 8 weeks, or its equivalent of 6000 IU/d of vitamin D\(_2\) or vitamin D\(_3\) followed by rechecking the serum 25(OH)
D level, followed by maintenance therapy of 1000 to 2000 IU/d (available over-the-counter) based on the results.\textsuperscript{101,105} For patients with 25(OH) D levels between 20 and 30 ng/mL, an alternative suggested by panel experts is to add an additional 1000 IU/d of over-the-counter vitamin D\textsubscript{2} or D\textsubscript{3} to the current intake and recheck the level periodically (Table 1).

Vitamin D toxicity (hypercalciuria, hypercalcemia, hyperphosphatemia, and activation of bone resorption) is very uncommon but may occur with massive daily doses of more than 50,000 IU/d that produce 25(OH) D levels of more than 150 ng/mL.\textsuperscript{101,105} Individuals with granulomatous disorders, such as sarcoidosis, tuberculosis, and chronic fungal infections, and some patients with lymphoma, may experience hypercalciuria and hypercalcemia when taking vitamin D supplements because of vigorous conversion of 25(OH) D to 1,25(OH)\textsubscript{2} D. These individuals may require a lower 25(OH) D target level of 20 to 30 ng/mL. Serum 25(OH) D and calcium levels must be carefully monitored in these individuals.

### Pharmacologic Agents for Bone Health

Several different classes of pharmacologic agents are approved by the FDA for the prevention or treatment of osteoporosis, including bisphosphonates, a receptor activator of nuclear factor κB ligand (RANKL) inhibitor (denosumab), selective estrogen receptor modulators (SERMs), calcitonin, and teriparatide.

#### Bisphosphonates: Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption, and several oral (alendronate, risedronate, and ibandronate) and intravenous bisphosphonates (ibandronate and zoledronic acid) are approved for prevention and/or treatment of osteoporosis. All except ibandronate are approved in both men and women. The efficacy of oral bisphosphonates in treating bone loss associated with endocrine therapy (AIs and ADT) has been demonstrated in a few small trials.\textsuperscript{106–108} Compliance is a significant problem with oral bisphosphonate dosing.\textsuperscript{109} The oral bisphosphonates are associated with esophagitis in susceptible patients, and therefore should be avoided in patients with esophageal emptying disorders or who are unable to sit upright, because these patients are at high risk for esophagitis.\textsuperscript{110} Both oral and intravenous bisphosphonates are valid options for patients with cancer, who are at risk for bone loss or fracture, or who have established osteoporosis.

**RANKL Inhibition:** RANKL is an essential cytokine that is expressed on the surface of osteoblastic cells and osteocytes. Denosumab is a human monoclonal antibody to RANKL that blocks osteoclast differentiation, proliferation, and function.\textsuperscript{111}

Denosumab is FDA-approved for the treatment of postmenopausal osteoporosis,\textsuperscript{111} for increasing bone mass in men with osteoporosis,\textsuperscript{112} and for the treatment of ADT and AI-induced bone loss\textsuperscript{113,114} at a dose of 60 mg subcutaneously every 6 months (Table 2). It is also approved for prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors at a dose of 120 mg monthly\textsuperscript{115,116} (Table 2).

**Estrogen/Hormonal Therapy:** Estrogen is an antiresorptive with proven antifracture efficacy, as demonstrated in the WHI study. Estrogen therapy alone and combined estrogen and progesterone were associated with a 33% to 34% reduction in hip fracture,
The same study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women. Because of these risks, the FDA recommends that estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen replacement therapy is not recommended in women with a history of breast cancer, including those who have had hormone receptor–negative disease, because of the increased risk of breast cancer recurrence.

In young patients with cancers other than breast cancer who experience chemotherapy-induced premature menopause, estrogen may be a treatment option for both menopausal symptoms and bone health. Data in young women with spontaneous premature ovarian failure argue against an increased risk of breast cancer or other adverse events with full replacement doses. Therefore, in women with chemotherapy-induced menopause who are not at increased risk for breast cancer, replacement of estrogen/progesterone until the normal age of menopause is not likely to produce the higher risk for adverse events seen in the WHI study, and is very likely beneficial for bone health.

**Selective Estrogen Receptor Modulators:** Although tamoxifen has a documented favorable impact on bone density in postmenopausal patients with breast cancer, raloxifene is currently the only SERM that is FDA-approved for preventing and treating osteoporosis in postmenopausal women. Raloxifene is a less-potent antiresorptive agent than bisphosphonates and denosumab. Raloxifene has been shown to decrease the incidence of vertebral fracture in postmenopausal women with osteoporosis; however, randomized studies have failed to document any benefit in terms of nonvertebral or hip fractures.

In the RUTH trial of postmenopausal women with a history of coronary artery disease and/or cardiovascular risk factors, raloxifene was associated with an increased risk of fatal stroke (hazard ratio [HR], 1.49; absolute risk increase 0.7 per 1000) and venous thromboembolism (HR, 1.44; absolute risk increase 1.3 per 1000). A decreased risk of invasive breast cancer was shown in the RUTH trial, confirming previous findings from an osteoporosis treatment trial and also from a trial of postmenopausal women at high risk for breast cancer.

### Table 2 The Dose and Frequency of Administration of Zoledronic Acid and Denosumab for Treating Osteoporosis, Preventing Bone Loss From Endocrine Therapies, and Preventing Skeletal-Related Events in Patients With Cancer

<table>
<thead>
<tr>
<th>Indication</th>
<th>Zoledronic Acid</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zometa (4 mg)</td>
<td>Reclast (5 mg)</td>
</tr>
<tr>
<td>Reduction in skeletal-related events due to advanced cancer involving the bone</td>
<td>√</td>
<td>–</td>
</tr>
<tr>
<td>Bone metastases (monthly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>√</td>
<td>–</td>
</tr>
<tr>
<td>Multiple myeloma (monthly)</td>
<td>√</td>
<td>–</td>
</tr>
<tr>
<td>Reduction in bone loss</td>
<td>√*</td>
<td>–</td>
</tr>
<tr>
<td>Al-induced bone loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADT-induced bone loss</td>
<td>√*</td>
<td>–</td>
</tr>
<tr>
<td>(every 3 mo or yearly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal osteoporosis</td>
<td>–</td>
<td>√</td>
</tr>
<tr>
<td>Prevention of postmenopausal osteoporosis (osteopenia (once every 2 y)</td>
<td>–</td>
<td>√</td>
</tr>
<tr>
<td>Men</td>
<td>–</td>
<td>√</td>
</tr>
<tr>
<td>Glucocorticoid therapy (yearly)</td>
<td>–</td>
<td>√</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen deprivation therapy; AI, aromatase inhibitor.

*This dose is not included in the FDA label for endocrine therapy–induced bone loss.
cancer. Hot flushes, leg cramps, peripheral edema, and gallbladder disease are more common with raloxifene than with placebo. The hot flashes induced by raloxifene may be accentuated in early menopause. Raloxifene use is not indicated in premenopausal women at high risk for breast cancer; in clinical trials of premenopausal women, both raloxifene and tamoxifen have been shown to cause a decrease in BMD.

The efficacy of raloxifene in combination with an AI for breast cancer remains unknown. In the ATAC trial, the concurrent use of tamoxifen (a SERM) and anastrozole had less antitumor efficacy than anastrozole alone. With this in mind, the combination of an AI and a SERM should not be used outside of a clinical trial. For women with a history of breast cancer, bisphosphonates or denosumab represent the best choices for preventing bone loss and/or treating established osteoporosis.

Parathyroid Hormone (1-34): Recombinant parathyroid hormone (1-34) or teriparatide is the first anabolic agent approved to treat postmenopausal osteoporosis. It has been shown to reduce the incidence of vertebral and nonvertebral fractures. Because of the potential increased risk for osteosarcoma, it is contraindicated in patients with an increased baseline risk of osteosarcoma, such as those with Paget disease of bone, open epiphyses, or prior radiotherapy involving the skeleton (which includes many patients with cancer). Furthermore, teriparatide is not indicated in patients with bone metastases. Although no data exist in patients with cancer, teriparatide is best avoided in patients with a history of malignancy prone to metastasize to bone. However, in cases of severe osteoporosis with fractures occurring on bisphosphonate therapy, the benefits may outweigh these theoretical risks. In patients with a remote history of cancer, teriparatide could be cautiously considered.

Calcitonin: Calcitonin, a hormone secreted by the C cells of the thyroid gland in response to elevations of the plasma calcium level, reduces bone resorption through inhibiting mature active osteoclasts, and increases renal calcium excretion. It is FDA-approved for the management of postmenopausal osteoporosis, Paget disease of bone, and malignancy-associated hypercalcemia. No studies have been performed using calcitonin to prevent bone loss in at-risk patients with cancer. The fracture risk reduction in patients with osteoporosis treated with calcitonin seems to be modest compared with that associated with the potent antiresorptive agents (bisphosphonates and denosumab). A meta-analysis of 30 studies concluded that calcitonin reduces the risk of vertebral fractures; however, its effect on nonvertebral fractures is uncertain. According to the FDA label, use of calcitonin nasal spray is recommended in conjunction with adequate calcium and vitamin D supplementation for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women and should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Calcitonin does not increase the risk of osteonecrosis of the jaw (ONJ) or atypical femoral fractures. In 2012, after reviewing the benefits and risks of calcitonin-containing medicines, the European Medicines Agency (EMA) concluded that evidence showed a small increased risk of cancer with long-term use of calcitonin. The EMA recommends calcitonin only for short-term use in Paget disease, acute bone loss from sudden immobilization, and hypercalcemia caused by cancer. An FDA advisory panel recently concluded that:

the potential risks of calcitonin (possibly a higher risk of various malignancies) do not outweigh its benefits as an osteoporosis drug; it is not recommended in the setting of bone loss due to cancer therapies except optionally for short term use post-acute osteoporotic vertebral fracture due to demonstrated analgesic effects in this setting.

Role of Antiresorptive Therapy in Maintaining Bone Health in Patients With Breast and Prostate Cancers
Several trials in cancer populations have studied SERMs and antiresorptive therapies (intravenous and oral bisphosphonates and denosumab) to prevent bone loss in vulnerable patients, such as those with breast cancer receiving AIs, those with chemotherapy-induced menopause or receiving other forms of ovarian suppression, those with prostate cancer undergoing ADT, and those with hematologic malignancy undergoing stem cell transplanta-
Many of these studies were small and assessed changes in BMD as a surrogate to osteoporotic fracture risk rather than fracture risk itself. Given that fracture risk independently increases with age, the goal of antiresorptive therapy in some relatively younger patients with cancer at risk for bone loss may be to prevent bone loss in the short term, and thereby preserve bone health and prevent potential future fractures in the long term. In patients with cancer, these studies have shown that antiresorptive therapy seems to be well tolerated, increase BMD, and decrease bone turnover markers. However, the trials conducted in cancer populations were not powered to address whether fracture risk is significantly reduced. In addition, dosing intervals of zoledronic acid other than every 6 months and optimal duration of therapy for any of these agents are open questions. In some oncologic patients, suppression of bone resorption markers may persist for years, whereas in others the effect does not persist.

**Postmenopausal Women Receiving AI Therapy:**
Several studies have analyzed the impact of antiresorptive therapy for maintaining bone density in patients undergoing AI treatment.

**Oral Bisphosphonates:** Two trials examined the effects of oral bisphosphonates in patients receiving anastrozole therapy. SABRE was an open-label intervention trial in which all patients who received anastrozole were assigned to treatment with oral risedronate based on T-scores. Patients with a low-risk T-score (> –1) received no intervention; patients with a T-score less than –2 received risedronate; and patients with a T-score between –1 and –2 were randomized to risedronate or placebo. For patients at low risk, bone loss during short-term follow-up was minimal. After 12 months, patients receiving anastrozole plus risedronate had a significant increase of 1.7%, and 1.3% from baseline BMD in their lumbar spine and hip, respectively. In contrast, patients on placebo lost 3.22% and 3.90% of their baseline BMD at the lumbar spine and hip, respectively.148 No data are available on BMD preservation in patients with normal baseline BMD for this study, because this group did not receive ibandronate.

**Intravenous Bisphosphonates:** The Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, and E-ZO-FAST) were designed to compare the effects of zoledronic acid (4 mg intravenously every 6 months) administered upfront concomitantly with AI (letrozole) therapy versus delayed administration at the first sign of bone loss (ie, T score < –2 or fracture). In the Z-FAST trial, results at 61 months indicate that the adjusted mean differences in lumbar spine and total hip BMD between the upfront and delayed groups were 8.9% and 6.7%, respectively (P < .0001, for both).149 The 12-month results from the E-ZO-FAST trial provide further evidence that upfront zoledronic acid not only prevents bone loss but also increases BMD, with a mean increase of 2.7% at the lumbar spine and 1.7% at the hip.150 The results of the final analysis of the ZO-FAST trial support early and continued use of zoledrionate during adjuvant therapy for breast cancer. At 60 months, the mean change in lumbar spine BMD was a gain of 4.3% with immediate zoledronate and a loss of 5.4% with delayed intervention (P < .0001).151

These studies suggest that both oral and intravenous bisphosphonates can mitigate the bone loss effects of AIs, although none of these trials have showed a statistically significant reduction in fractures to date. No clinical trials have directly compared oral versus intravenous bisphosphonates in this setting.

**Denosumab:** A randomized, double-blind, placebo-controlled phase III trial evaluated the effect of denosumab in patients receiving adjuvant AI therapy. Patients with early-stage, hormone receptor–positive breast cancer were randomized to either denosumab at 60 mg or placebo every 6 months for a total of 4 doses while receiving AI therapy. At 12 and 24 months, lumbar spine BMD increased by 5.5% and 7.6%, respectively, in the denosumab group compared with the placebo group (P < .0001). After 24 months on therapy, the BMD increases in the total hip, femoral neck, trochanter, and radius were 4.7%, 3.5%, 5.9%, and 6.1%, respectively.114

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Premenopausal Women With Therapy-Induced Ovarian Suppression/Failure: Several studies reported that bisphosphonates, including zoledronic acid, pamidronate, clodronate, and risedronate, attenuate the bone loss associated with treatment-related ovarian failure. Zoledronic acid has been studied in several trials. In one trial, premenopausal patients undergoing chemotherapy with several regimens were randomized to either receive treatment with zoledronic acid or placebo every 3 months for 1 year. Women who received zoledronic acid had significantly less bone loss. In addition, updated results showed that prevention of bone loss persisted up to a year after completion of therapy. BMD remained stable in patients treated with zoledronic acid (P<.0001 vs placebo), whereas the lumbar spine BMD decreased from baseline by 5.5% at 12 and 6.3% at 24 months in individuals receiving placebo.

In CALGB 79809 study, premenopausal patients beginning adjuvant chemotherapy were randomized to receive either early zoledronic acid (4 mg every 3 months) or delayed zoledronic acid (given 1 year after adjuvant chemotherapy). The primary end point was change in lumbar spine BMD. Bone density was preserved in patients treated with early zoledronic acid at 12 months, compared with a 6.6% loss of BMD in the lumbar spine at 1 year reported for patients who did not receive zoledronic acid until 1 year after their adjuvant chemotherapy began (delayed group).

Bisphosphonates are also effective for minimizing loss of BMD in women receiving ovarian suppression with GnRH. In the ABCSG-12 trial, the effect of adding zoledronic acid was examined in premenopausal patients with early breast cancer treated with ovarian suppression plus anastrozole or tamoxifen. Ovarian suppression with goserelin plus tamoxifen or anastrozole for 3 years without concomitant zoledronic acid caused significant bone loss. After 2 years of completing treatment, a partial recovery of BMD was seen in these patients; however, the recovery level was lower than their baseline BMD. The addition of the bisphosphonate prevented bone loss in both the lumbar spine and hip. Patients who received zoledronic acid had stable lumbar spine BMD at 36 months and increased lumbar spine BMD at 60 months. Additionally, treatment with zoledronic acid resulted in fewer breast cancer recurrences (see “Role of Adjuvant Antiresorptive Agents in Preventing Recurrence,” page S-15). Although results of studies showing the ability of bisphosphonates to preserve BMD in young women with treatment-related ovarian failure are encouraging, no study to date has shown an impact on the clinically relevant end point of fractures.

Men Receiving ADT: Men who receive ADT experience more rapid rates of bone loss than normal and may be at high risk for fragility fractures (Figure 2). Therefore, effective and evidence-based management of bone loss in patients with prostate cancer receiving ADT is important. A DXA scan to determine baseline BMD should be considered for all men commencing ADT.

Bisphosphonates: Small randomized controlled trials have shown that bisphosphonate treatment during ADT increases BMD, a surrogate for fracture risk. These studies were limited by small sample size and were not powered to detect differences in fracture risk between the groups. Additionally, these studies used a variety of agents and dosing schedules.

In a 12-month multicenter placebo-controlled study of 106 men with prostate cancer, intravenous zoledronic acid every 3 months increased BMD of the hip and spine by a difference of 3.9% and 7.8%, respectively. Similar results have been reported with annual zoledronic acid. With a single annual dose of zoledronic acid, the mean BMD of the lumbar spine and hip increased by 4.0% and 0.7%, respectively, in men receiving zoledronic acid. In contrast, the mean BMD of the spine and hip decreased by 3.1% and 1.9%, respectively, with placebo. Intravenous pamidronate and zoledronic acid given once every 3 months prevented ADT-induced bone loss in the spine and hip compared with control groups. In contrast to pamidronate, zoledronic acid increased BMD. Mean lumbar spine BMD was increased by 5.6% in men receiving zoledronic acid (n=42) but decreased by 2.2% in the placebo group (n=37). Zoledronic acid therapy has also been found to be effective when initiated later during the course of ADT. In patients randomized to 4 mg of zoledronic acid intravenously every 3 months for 4 treatments, the BMD at the spine increased by 5.95% and, in contrast, decreased by 3.23% in the placebo arm (P=.0044).

In a randomized controlled trial of 112 men with nonmetastatic prostate cancer receiving ADT, 70 mg of weekly oral alendronate increased BMD of the hip and spine by 2.3% and 5.1%, respectively, after 12 months. 158 Also, bone density was pre-
In a recently reported trial, patients who received 70 mg weekly of oral alendronate had an increase of 1.7% in their mean spine BMD compared with a decrease of 1.9% in those who received placebo (P<0.0001). In a meta-analysis including 2634 men with prostate cancer, treatment with bisphosphonate therapy had a substantial effect in preventing fractures and osteoporosis. Although long-term data regarding the impact of bisphosphonates on fracture prevention are not available, these studies provide evidence that bisphosphonates effectively reduce bone loss and may prevent fracture in men receiving ADT.

Selective Estrogen Receptor Modulators: Several small randomized controlled trials have shown that SERMs increase BMD in men receiving ADT for prostate cancer. Treatment with raloxifene increased BMD of the hip and lumbar spine after 1 year compared with placebo in patients with prostate cancer receiving ADT. Toremifene, a SERM approved for the treatment of advanced breast cancer, increased BMD of the hip and spine in men receiving ADT for prostate cancer. In a large multicenter study, 1284 men in the United States and Mexico receiving ADT for prostate cancer were randomly assigned to either toremifene or placebo. Toremifene also significantly increased BMD at the lumbar spine, hip, and femoral neck and decreased bone turnover markers compared with placebo. In addition, toremifene significantly reduced fracture risk by 50% compared with placebo at 2 years. However, treatment with toremifene was associated with an increased rate of venous thromboembolic events compared with placebo (2.6% vs 1.1%, respectively).

Denosumab: The effects of denosumab on bone loss and incidental vertebral fractures were investigated in the large, randomized, placebo-controlled phase III HALT trial involving 1468 men with prostate cancer at increased risk of fracture (given age ≥70 years, low BMD defined as a T score < −1, or a history of an osteoporotic fracture) receiving ADT. Denosumab at 60 mg versus placebo was administered subcutaneously every 6 months for 2 years. Mean lumbar spine BMD at 24 months was increased by 5.6% with denosumab compared with a 1.0% loss with placebo (P<0.001). The BMD at the total hip, femoral neck, and distal one-third of the radius was also significantly increased with denosumab versus placebo. Patients treated with denosumab had a decreased incidence of new vertebral fracture at 12, 24, and 36 months. The 3-year risk of new vertebral fractures was reduced by 62% with denosumab (P=0.006 vs placebo). In a further subgroup analysis of this study, denosumab significantly increased BMD at all measured skeletal sites for every subgroup analyzed, including older men and those with prevalent fractures considered at greatest risk of fracture. The rates of adverse events were similar between the groups. Hypocalcemia was seen in 1 person in the treatment arm versus none in the placebo arm. No cases of ONJ were documented in either group.

NCCN Recommendations for Maintaining Bone Health During Cancer Therapy

The rate and magnitude of bone loss caused by cancer therapy is significantly higher than normal age-related bone loss (Figure 2). Therefore, it is vital to maintain BMD and prevent fractures in these patients. However, bone density monitoring and intervention strategies should be individualized, with drug therapy reserved for patients at greatest risk.

Initial strategies to reduce morbidity associated with bone loss caused by cancer therapy include educating patients about the risks, encouraging healthy lifestyle modifications, and supplementation with calcium if necessary (to achieve a total intake from food plus pills equal to 1200 mg/d) and vitamin D3 (800–1000 IU/d) for all adults older than 50 years. The NCCN Task Force recommends these same ranges for younger patients at risk for cancer treatment–associated bone loss. Given that vitamin D deficiency or insufficiency, with or without secondary hyperparathyroidism, is common among patients with cancer, many patients may need more than the recommended amount of vitamin D. In patients with risk factors for vitamin D deficiency or in those with low BMD, serum 25(OH)D levels should be measured and repletion performed according to this level (Table 1). It is prudent to measure urinary calcium excretion and other markers of lithogenic risk in patients with a history of calcium nephrolithiasis.

The task force strongly recommends initiating pharmacologic therapy to lower fracture risk if the T score is less than or equal to −2.0 at the lumbar spine, femoral neck, or total hip sites or if the FRAX 10-year absolute risk of fracture is greater than 20% for any major fracture or greater than 3% for hip fracture, respectively. In addition, the panel recommends considering pharmacologic therapy for indi-
individuals with T score less than –1.5 who have lost significant BMD as a result of their cancer therapy (Figure 1).

In women treated with AIs, even if annual bone loss returns to the postmenopausal rate after cessation of therapy, loss of BMD during treatment is significantly higher compared with their healthy counterparts. Earlier intervention may be beneficial to reduce the skeletal problems and preserve patient quality of life.\textsuperscript{149–151,166,167} Emerging data suggest a benefit to longer duration (additional 5 years) of tamoxifen as adjuvant endocrine therapy.\textsuperscript{168} If recommending longer durations of adjuvant tamoxifen therapy, clinicians should bear in mind that although tamoxifen has shown a favorable effect on bone density in postmenopausal women, it induces bone loss in premenopausal women.\textsuperscript{169,170}

Bisphosphonates and now denosumab are established antiresorptive therapies for preserving bone health of patients with early-stage breast cancer who are at high risk for fracture. However, currently no data exist on their effect on fracture rates in these patients. Treatment recommendations are mostly based on expert guidance, relatively small studies in cancer patients, and extrapolation of results from studies in postmenopausal women with osteoporosis. Oral bisphosphonates have shown encouraging results,\textsuperscript{108,171} however, patient compliance with treatment outside the clinical trial setting must be considered with these drugs. Several retrospective analyses revealed increased risk of fracture in noncompliant patients, and tangible benefits in compliant patients.\textsuperscript{109,172–175} For noncompliant patients, intravenous/subcutaneous antiresorptive agents may be preferable.

For men receiving ADT who are at high risk of fracture and warrant pharmacologic treatment, consensus is lacking regarding the treatment agent, dose, and schedule. Currently, denosumab (60 mg subcutaneously every 6 months) is the only FDA-approved agent to increase bone mass and prevent fracture in high-risk men receiving ADT for prostate cancer. Other pharmacologic treatments to consider for ADT-associated bone loss include zoledronic acid at 4 mg intravenously every 3 months, zoledronic acid at 4 mg intravenously yearly, and alendronate at 70 mg orally weekly. Given that use of these agents was not investigated beyond a maximum of 2 years, limited data exist regarding duration of therapy.

Role of Adjuvant Antiresorptive Agents in Preventing Recurrence

The antiresorptive agents (bisphosphonates and denosumab) have an established role as preventative and therapeutic agents for the management of osteoporosis, hypercalcemia of malignancy, and bone metastases from solid tumors and multiple myeloma. Evidence from preclinical studies in breast cancer models suggests that bisphosphonates may improve survival outcomes in patients with cancer because of their documented antitumor activity,\textsuperscript{176–180} including prevention of tumor cell adhesion to bone,\textsuperscript{185,181} induction of tumor cell apoptosis,\textsuperscript{178} blocking of the interaction between mesenchymal stem cells and breast cancer cells,\textsuperscript{176} and inhibition of angiogenesis.\textsuperscript{182} Animal studies have shown that pretreatment of nude mice with bisphosphonates before inoculation of tumor cells reduces the development of osteolytic lesions.\textsuperscript{183} Taken together, these studies suggest that, in addition to their antiresorptive action, antiresorptive agents may inhibit critical steps in the development of bone metastases, which has implications for adjuvant therapy for breast cancer.

Breast Cancer Recurrence

Clodronate: Four randomized trials in patients with early-stage breast cancer investigated whether oral clodronate can prevent bone metastases and improve survival, and have reported mixed results, with variable effects on disease-free survival and overall survival (OS).

In a large placebo-controlled trial, 1069 patients with breast cancer receiving standard systemic therapies were randomized to receive oral clodronate (1600 mg/d) or placebo for 2 years as adjuvant treatment.\textsuperscript{184} This trial reported a reduced risk of bone metastases with clodronate: 51 versus 73 events (HR, 0.69; \( P = .04 \)) at 5 years, and 19 versus 35 events (HR, 0.55; \( P = .048 \)) during the 2 years on treatment. Survival at 5 years, the preplanned study end point, favored the clodronate group with an HR of uncertain significance because of multiple analyses (HR, 0.77; \( P = .048 \)). The most recent reporting includes survival data with long-term follow-up, which showed a continued separation of the survival curves between years 5 and 10.\textsuperscript{185}

In a second smaller, randomized, open-label study, 302 women with breast cancer and micrometastases detected in a bone marrow aspirate at diag-
nosis were randomized to receive either clodronate (1600 mg/d) or no bisphosphonate for 2 years. Additionally, patients received standard adjuvant systemic therapy. Patients who received clodronate had a 50% reduction in the incidence of bone metastases (P=.003), and a significantly longer bone metastasis–free survival (P<.001). Distant metastases were detected in 21 of 157 patients (13%) who received clodronate compared with 42 of 145 patients (29%) in the control group (P<.001). A later analysis at 8.5 years of follow-up continued to confirm a significant improvement in OS for patients treated with clodronate, although the significance in disease-free survival no longer persisted.

Results of a third small, randomized, open-label study investigating 3 years of adjuvant clodronate therapy in 299 patients with lymph node–positive breast cancer showed no reduction in bone metastases in the clodronate-treated arm, although bone as a first site of relapse was less frequent in the clodronate group than in controls (14% vs 30%). However, a worrisome increase in visceral metastases and a reduction in OS at 5 years were seen in patients receiving clodronate. A possible explanation for these adverse outcomes is an imbalance in hormone-negative cases between the arms of the study, with the clodronate group showing significantly more progesterone receptor (PR)–negative tumors (45% vs 31%; P=.03) and a trend toward more estrogen receptor (ER)–negative (35% vs 23%) tumors. This difference was potentially exacerbated by the practice in this trial of assigning endocrine therapy alone to all postmenopausal women and chemotherapy alone to all premenopausal women, regardless of ER/PR status. The negative impact of clodronate on OS seems to be neutralized when the imbalance in hormone receptor negativity is corrected. Even without correction, the survival detriment no longer showed significance at 10 years.

A meta-analysis using the 5-year data from these 3 adjuvant clodronate trials did not show a statistically significant difference in OS or bone metastasis–free survival when the data were pooled. Marked heterogeneity was noted among the trials that partly explains the wide confidence interval around the HR (HR, 0.75; 95% CI, 0.31, 1.82).

The fourth trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34, randomized 3323 patients with stage I–III breast cancer to oral clodronate for 3 years or placebo, given alone or in addition to adjuvant chemotherapy or hormone therapy. More than two-thirds of the patients were older than 50 years and had ER-positive tumors. The median follow-up at final analysis was 8.41 years. The long-term results showed no difference in disease-free survival (HR, 0.913; P=.266) between the groups. Importantly, treatment compliance was poor, with only 42% of patients completing the assigned study therapy. Examination of the secondary end points showed a significant difference in favor of clodronate with respect to the metastasis-free interval (HR, 0.743; P=.046). In addition, a hypothesis-generating subgroup analysis showed that women older than 50 years derived more benefit from clodronate than did younger women. Disease-free survival was similar in older versus younger women, but improvements in skeletal metastasis–free interval (P=.027) and nonskeletal metastasis–free interval (P=.014) were noted with clodronate in women aged 50 years or older. Patients older than 60 years appeared to derive the most benefit from adjuvant clodronate, including an almost 60% reduction in skeletal metastases and a 40% to 50% reduction in nonskeletal metastases.

**Ibandronate:** The German Adjuvant Intergroup Node-Positive (GAIN) trial randomized 3023 patients to a standard regimen of epirubicin, paclitaxel, and cyclophosphamide with or without capecitabine. The patients were further randomized 2:1 to 2 years of treatment with oral ibandronate (50 mg/d orally) or observation. The results showed no effect of ibandronate treatment on disease-free survival or OS in patients with node-positive, early breast cancer treated with dose-dense chemotherapy.

**Zoledronic Acid:** The Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) enrolled 1800 premenopausal women with ER-positive breast cancer. All patients received ovarian suppression for 3 years with a luteinizing hormone–releasing hormone analogue, goserelin. Patients were randomized in a 2 × 2 design to receive tamoxifen versus anastrozole, and zoledronic acid (4 mg every 6 months for 3 years) or not. In ABCSG-12, the zoledronic acid dose was initially 8 mg every 4 weeks, and then was reduced to 4 mg every 6 months after a protocol amendment in 2000. At the first efficacy analysis, reported after 137 events (70 distant relapses) with approximately 60 months of follow-up,
no difference in outcome was seen with respect to the endocrine therapy randomization. However, a statistically significant improvement in disease-free survival was seen for the patients who received zoledronic acid (HR, 0.64; \( P = .01 \)), with a trend toward improved OS (HR, 0.60; \( P = .10 \)). The absolute benefit in disease-free survival was 3.2%. The results after 76 months of follow-up showed that patients receiving zoledronic acid had a 27% reduction in the risk of disease-free survival events (HR, 0.73; \( P = .022 \)) and a 41% reduction in the risk of death (HR, 0.59; \( P = .027 \)) when compared with patients who did not receive zoledronic acid. Multivariate analysis showed a strong interaction between zoledronic acid and patient age. Among patients older than 40 years, zoledronic acid significantly reduced the risk of recurrence by 34% (HR, 0.66; \( P = .014 \)) and the risk of death by 49% (HR, 0.51; \( P = .020 \)). However, no improvement was seen in either disease-free or OS survival in this post hoc analysis among patients younger than 40 years. The ABC-SG-12 study enrolled a narrow subset of patients with breast cancer: premenopausal women with ER-positive tumors who did not receive adjuvant chemotherapy. Although the results are promising, clinicians must be cautious not to overextrapolate these findings, or this dose schedule, to all patients with breast cancer.

In the AZURE trial, 3360 patients with node-positive (N1) or T3–T4 breast cancer were randomized to receive standard adjuvant systemic therapy with or without zoledronic acid. This study did not select patients according to menopausal or ER status, although most of the patients (78%) enrolled were ER-positive. Zoledronic acid was administered as 4 mg every 3 to 4 weeks for 6 cycles and then every 3 months for 8 doses, followed by 5 cycles on a 6-month schedule for a total of 5 years. This trial showed no benefit in disease-free survival in patients treated with zoledronic acid compared with those treated without (HR, 0.98; CI, 0.85–1.13; \( P = .79 \)). In a prespecified subgroup analysis of postmenopausal patients, the rates of invasive disease–free survival were 78.2% in the zoledronic acid group versus 71% in the control group (HR, 0.75; CI, 0.59–0.96; \( P = .02 \)). Additionally, for patients in whom menopause had occurred more than 5 years before study entry, the 5-year OS was 84.6% in the zoledronic acid group and 78.7% in the control group (HR, 0.74; CI, 0.55–0.98; \( P = .04 \)), compared with all other patients, for whom the rates were 74.1% in the zoledronic acid group and 77.2% in the control group (adjusted HR, 1.15; 95% CI, 0.97–1.36; \( P = .11 \)). These results suggest a possible systemic effect of zoledronic acid that operates differently according to menopausal status.

Three large, very similar studies in ER-positive postmenopausal women receiving AIs (Z-FAST,\(^{149}\) ZO-FAST,\(^{151,166}\) and E-ZO-FAST\(^{150}\) ) compared the efficacy of zoledronic acid (4 mg every 6 months for 5 years) given either at the start of AI therapy, “upfront,” or after documented bone loss or development of a nontraumatic fracture, “delayed”. All 3 studies showed that immediate zoledronic acid prevented bone loss,\(^{149,150,166}\) In the Z-FAST study, small differences in disease recurrence or death were observed between the groups at months 12, 24, 36, and 48 in favor of the upfront group; however, rates at month 61 were similar between the groups (upfront, 9.8% [range, 6.0%–10.3%]; delayed, 10.5% [range, 6.6%–14.4%]; \( P = .6283 \)).\(^{149}\) A 60-month follow-up of the ZO-FAST study showed a 34% (HR, 0.66; \( P = .0375 \)) improvement in disease-free survival with “upfront” zoledronic acid compared with “delayed” therapy.\(^{151}\)

Zoledronic acid seems to have a different effect in patients with high versus low estrogen environments (post- vs premenopausal patients), which needs confirmation in future trials. A meta-analysis of data from 8735 women in 7 adjuvant bisphosphonate trials (AZURE, ABCSG-12, ZO-FAST, Z-FAST, E-ZO-FAST, NSABP-B34, GAIN), including only those known to be aged 50 years or older, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer.\(^{193}\) The Early Breast Cancer Trialists’ Collaborative Group (EBTCG; Oxford Overview) is currently conducting a formal meta-analysis of all randomized adjuvant bisphosphonate studies, which should contribute substantially to the understanding of which populations of patients with early-stage breast cancer will benefit from the addition of adjuvant bisphosphonates.

Several additional ongoing early-stage bisphosphonate trials are evaluating various agents, doses, schedules, and settings, including residual disease after preoperative chemotherapy and elderly populations. SWOG S0307 (ClinicalTrials.gov identi-
fier: NCT00127205) randomized 6000 patients with stage I–III breast cancer receiving standard adjuvant therapy to oral clodronate (1600 mg/d) versus oral ibandronate (50 mg/d) versus zoledronic acid (4 mg intravenously monthly for 6 months, then every 3 months), all for 3 years duration. This currently unreported trial included both pre- and postmenopausal women, ER-positive and -negative tumors, and patients who received a range of standard systemic therapy, including chemotherapy. The results of SWOG S0307 and other trials will be critical in determining how broadly applicable bisphosphonates are across the spectrum of patients with breast cancer.

Denosumab: In the adjuvant setting, an ongoing phase III clinical trial (D-CARE: Study of Denosumab as Adjuvant Treatment for Women With High Risk Early Breast Cancer Receiving Neoadjuvant or Adjuvant Therapy) is investigating the ability of denosumab to prolong skeletal metastases–free survival and disease-free survival in women with stage II–III breast cancer who are at high risk for recurrence.194 Additionally, the ABCSG-18 trial is randomizing postmenopausal patients treated with adjuvant AIs to either denosumab or placebo.

Prostate Cancer Recurrence

In prostate cancer, trials have yet to show any reduction in recurrences or deaths from the adjuvant use of bisphosphonates. A randomized controlled trial to evaluate the effects of zoledronic acid on time to first bone metastasis in men with prostate cancer without bone metastases and a rising prostate-specific antigen (PSA) level despite ADT was terminated approximately halfway into accrual when interim analysis showed a lower-than-expected event rate.195 A randomized, double-blind, placebo-controlled trial of oral clodronate versus placebo in patients with nonmetastatic prostate cancer found no differences in bone metastases–free survival or OS after nearly 10 years of follow-up.196

A double-blind, randomized, placebo-controlled study, in men with nonmetastatic castration-resistant prostate cancer at high risk for bone metastasis evaluated subcutaneous denosumab at 120 mg versus subcutaneous placebo every 4 weeks in extending bone metastasis–free survival. Results showed that denosumab increased bone-metastasis-free survival by a median of 4.2 months compared with placebo and also delayed time to first bone metastasis.197 OS did not differ between groups (denosumab, 43.9 months [95% CI, 40.1–not estimable] vs placebo, 44.8 months [95% CI, 40.1–not estimable]; HR, 1.01; 95% CI, 0.85–1.20; P = .91).

A subsequent analysis of this trial found that for patients with a PSA doubling time of 6 months or less, the median time to bone metastases was 25.2 months with denosumab versus 18.7 months with placebo (HR, 0.77; 95% CI, 0.64–0.93).198 This study provides clinical evidence that targeting of the bone microenvironment can delay bone metastasis in men with prostate cancer. However, the FDA advisory panel recommended against expanding the indications for denosumab as a prophylactic agent against bone metastases in castration-resistant nonmetastatic prostate cancer.

Several ongoing trials are evaluating the adjuvant use of osteoclast-targeted therapy in prostate cancer. One of the objectives of the Randomized Androgen Deprivation and Radiotherapy (RADAR) trial is to determine whether 18 months of zoledronic acid will reduce relapse risk through impeding the development of bony metastases (ClinicalTrials.gov identifier: NCT00193856). The ZEUS trial (ClinicalTrials.gov identifier: ISRCTN66626762) is designed to assess the efficacy of zoledronic acid every 3 months versus best supportive care in the prevention of skeletal metastases in patients with high-risk prostate cancer. However, after a median follow-up of 50 months, the results of the ZEUS trial presented at the Annual European Association of Urology Congress showed no difference in the incidence of bone metastases or survival between the zoledronic acid group and the control arm.199 Denosumab is being tested in an ongoing large, international, randomized, placebo-controlled, phase III trial in men with hormone-refractory prostate cancer with an end point of bone metastasis-free survival (ClinicalTrials.gov identifier: NCT00286091).

Summary and NCCN Recommendations

The adjuvant bisphosphonate trials in breast cancer reported to date support the potential role of the antiresorptive drugs in impacting recurrence and survival in early-stage breast cancer. The promising yet somewhat contradictory results of the 4 reported clodronate studies and data on adjuvant zoledronic acid from AZURE and ABCSG-12 suggest that bisphosphonates can impact disease recurrence, but highlight the need for further investigation.
The greatest benefit of adjuvant bisphosphonates seems to be for postmenopausal women and premenopausal women receiving endocrine therapy that includes ovarian suppression. Whether doses used in metastatic disease are required for prevention or whether lower doses will suffice is unknown. Still unclear are whether adjuvant bisphosphonates should be given continuously and orally, whether “less intensive” intravenous regimens will turn out to be as effective as “more-intensive” regimens. The optimal duration of adjuvant bisphosphonate therapy is also unknown. Available data do not yet support the addition of adjuvant bisphosphonates as standard of care for patients with breast cancer. Because of many outstanding questions, use of adjuvant bisphosphonates in early-stage breast cancer to reduce recurrence and improve survival is currently considered investigational.

No bisphosphonate has shown benefit in preventing bone metastases in men with prostate cancer. Denosumab has been shown to delay the onset of bone metastases in patients with castration-resistant prostate cancer, although the clinical significance of this has yet to be determined. The NCCN Task Force does not recommend the use of osteoclast-targeted therapy for preventing bone metastases from prostate cancer.

**Bone Metastases**

Bone is a common site for metastases of breast, prostate, and lung cancers, and renal cell carcinoma and others. In multiple myeloma, bone is the predominant organ involved. Estimates (based on a commercially insured cohort of patients) show that 280,000 adults in the United States are living with metastatic bone disease. Patients with breast, prostate, and lung cancers account for 68% of these cases.

**Pathophysiology of Bone Metastases**

The development of bone metastases is a multi-step process that includes the following sequence of events: growth of tumor cells at the primary site, detachment of the cancer cells, invasion of cancer cells through the tissue stroma and into the vasculature, survival of the cancer cells in circulation, extravasation and attachment of the circulating tumor cells to the bone marrow (seeding or homing), leading to the establishment of metastatic microenvironment with its associated cross-talk between cancer cells and bone cells (colonization), and induction of angiogenesis, thereby permitting increased tumor cell survival and proliferation in the bone (expansion). The concept of the “premetastatic niche” has been suggested by preclinical studies and seems to involve bone and bone marrow–derived hematopoietic cells “preparing” sites of future metastases and recruiting tumor cells through protein interactions involving integrins such as CXCL12-CXCR4. The tumor invasion into the bone results in the release of growth factors from stromal cells and the bone microenvironment, many of which positively regulate tumor growth, leading to a vicious cycle.

In patients with early-stage breast cancer or with prostate cancer, disseminated tumor cells (DTCs) may be identified in the bone marrow of patients who do not have frank metastases. Similarly, circulating tumor cells (CTCs) may be identified in patients with early-stage breast cancer. DTCs have been detected in bone marrow in up to 30% to 40% of patients with breast cancer without detectable metastases at the time of primary diagnosis. Although DTC status at diagnosis is a prognostic marker for the risk of metastases, it has been observed that a substantial number of DTC-positive patients never have disease recurrence. Recently, detection of persistent DTCs after definitive therapy has been shown to identify patients at higher risk for relapse. Although DTCs and CTCs are associated with an increased risk of cancer recurrence, not all patients with DTCs or CTCs develop metastases. The state of tumor cell dormancy, quiescence, or latency and its relationship to cancer progressing to symptomatic disease is an active area of research.

Metastatic bone disease is often classified based on radiographic appearance using the spectrum of findings from osteoblastic to osteolytic. On imaging, metastatic bone disease associated with breast cancer is often predominantly osteolytic, whereas lesions from prostate cancer are predominantly osteoblastic. This distinction is not absolute, bone metastases are frequently heterogeneous, and, on histologic examination, evidence is often seen of both osteolytic and osteoblastic features. Regardless of the imaging or histologic features of the bone metastases, tumor in bone is associated with significant morbidity and mortality.
Osteoclasts degrade the bone matrix, thereby liberating cytokines and growth factors harbored within the bone. Macrophage colony-stimulating factor and RANKL are produced by osteoblasts, and may also be produced by tumor cells. Stimulation of the RANK receptor by RANKL induces osteoclast activation and formation. In addition, tumor cells commonly produce parathyroid hormone protein and interleukins, which in turn activate RANKL secretion from osteoblasts.\(^{216}\) Additionally, multiple pathways activated by the tumor cells can contribute to osteoclast differentiation. For example, secreted matrix metalloproteases (MMPs) play an important role in osteolysis; MMP7 cleaves and activates RANKL, whereas MMP1 decreases levels of osteoprotegerin (OPG), the decoy receptor and inhibitor of RANKL.

Multiple pathways may be activated during tumor progression within bone. Tumor cells can secrete the WNT protein, which is central to osteoblast differentiation during bone metastases and plays a role in activating multiple downstream genes, including transcription factors such as RUNX-2, a key regulator of osteoblasts. Tumor cells in bone may stimulate osteoblast activity through the secretion of additional factors, including bone morphogenic proteins, insulin growth factors, fibroblast growth factors, and endothelin-1.\(^{203}\) Tumor cells may also secrete factors that indirectly influence osteoblast activity, including vascular endothelial growth factor, which can activate osteoblasts and induce angiogenesis.\(^{217-219}\) These factors may induce tumor cell proliferation, thereby generating a vicious cycle of tumor growth and bone destruction.\(^{220}\) Novel therapies are under investigation to alter these and other signaling pathways in attempt to alter the course of the tumor.

**Complications of Bone Metastases**

The clinical course of metastatic bone disease varies based on the primary tumor and response to therapy. In conditions such as multiple myeloma or metastatic breast or prostate cancers, the life expectancy of patients with bone metastases is typically measured in years. This highlights the importance of managing bone metastases from the onset of diagnosis to reduce the risk of skeletal complications associated with malignancy. Other metastatic cancers may have a shorter life expectancy, yet optimizing bone care is just as important. The clinical complications of bone metastases include debilitating bone pain, which tends to be most prominent with movement, pathologic fractures, spinal cord compression with its associated pain and neurologic complications, hypercalcemia of malignancy, and bone marrow infiltration with associated suppression of hematopoiesis. The term SREs refers to a constellation of skeletal complications, including fracture, need for surgery on bone, need for radiation to bone, spinal cord compression, and, in some situations, hypercalcemia of malignancy. In clinical trials examining antiresorptive agents, SREs are frequently used as a clinical end point. In addition, bone pain, analgesic use, and quality of life (QOL) are also often used as clinical trial end points when examining therapies for managing bone metastases.

Metastatic bone disease is responsible for severely compromising a patient’s QOL and adding significantly to their morbidity and mortality.\(^{205,221}\) As indicated by studies using Medicare claims, the presence of bone metastases is strongly associated with mortality among patients with breast and prostate cancers.\(^{222,223}\) SREs occurred in 46% of women\(^{222}\) and 44% of men\(^{223}\) with bone metastases. The mortality rate was higher in those with bone metastases complicated by SREs than in those with bone metastases without SREs.\(^{222,223}\)

SREs not only compromise QOL and increase mortality of patients with metastatic bone disease but also carry a significant economic burden.\(^{224}\) Management of SREs in patients with bone metastases can be a major cause of hospitalization and expenditure of health care resources.\(^{225}\)

**Imaging of Bone Metastases**

Common sites for skeletal metastases are the vertebrae, pelvis, proximal parts of the femur, ribs, proximal part of the humerus, and skull. Imaging plays an important role in the detection, diagnosis, treatment planning, and follow-up monitoring of bone metastases. If bone metastases are suspected and/or present, imaging the skeleton is useful for screening to confirm diagnosis and assessing the extent of metastatic disease. The response to therapy can be evaluated through radiographs (plain films) and correlating the radiographic changes with bone scan findings, and through clinical and laboratory findings.

Numerous imaging techniques are available to evaluate bone metastases, including plain film radiography, CT, MRI, technetium-99m (\(^{99m}\)Tc) bone scanning (ie, radionuclide bone scan), PET both with fluorodeoxyglucose (FDG) and with 18F sodium fluoride, and single-photon emission CT (SPECT).
Imaging Techniques to Evaluate Bone Metastases

**Radiography:** Plain film radiography, the oldest imaging technique for evaluating bone metastases, recognizes alterations in bone density, such as osteolytic and osteoblastic changes. In the case of an indeterminate bone scan finding, a plain film may be helpful for further characterizing a suspicious lesion. In the setting of bone pain, plain films may be helpful in detecting the cause. In patients with one or few sites of skeletal pain, targeted radiographs may be used for initial imaging. Plain films can assess cortical destruction by the cancer, providing valuable information regarding fracture risk. Unfortunately, plain films are relatively insensitive for detecting early or small metastatic lesions. To recognize an osteolytic lesion on a plain film, a 30% to 50% loss in bone density must occur.\(^{227}\)

**CT:** CT, like plain films, is a map of bone density, with a tomographic capability. Compared with plain films, CT images have an improved target-to-background ratio and improved sensitivity. CT has been found to be more sensitive than plain film radiography in detecting metastatic lesions.\(^{228,229}\) CT is used to assess lesion size and cortical reaction. CT is useful for guiding needle biopsy of lesions in bones with complex shapes, such as the vertebrae. CT can also identify alterations in adjacent soft tissue. As with plain films, CT is useful for characterizing suspicious lesions that might be present on a bone scan. The usefulness of CT in detecting early involvement of the bone marrow, however, is limited. Although CT scanning is superior to radiography, some advanced destructive lesions of the cancellous bone may not be visible on CT scans, particularly in the absence of reactive new bone or cortical involvement. In addition, skeletal coverage is limited with CT because of its relatively high radiation dose, making CT unsuitable as a screening tool.

**MRI:** MRI is associated with a high sensitivity (82%–100%) and specificity (73%–100%) for bone marrow metastases. Unlike CT and plain film, MRI does not assess bone density, but is helpful in assessing tissue alterations. Therefore, MRI can detect metastases that have infiltrated bone marrow\(^{230}\) before they provoke an osseous bone response. MRI is more sensitive for detecting early lesions and marrow-based metastases than are plain films, CT, or radionuclide bone scans.\(^{231,232}\) It has higher spatial resolution than bone scintigraphy and has a quantitative capability. Although MRI is a good choice for detecting marrow infiltration, its role in bone metastases is generally limited because it is more expensive and not as readily available as CT.\(^{227}\)

Diagnostic whole-body MRI is a clinically feasible alternative to \(^{99m}\)Tc planar bone scintiscanning in evaluating the entire skeleton for metastatic disease.\(^{233,234}\) Whole-body MRI takes 40 to 45 minutes to perform and involves the use of short-tau inversion recovery (STIR) and/or T1-weighted sequences.\(^{235}\) In a relatively small study comparing whole-body MRI with PET/CT,\(^{235}\) whole-body MRI had slightly higher sensitivity and specificity (95% and 92%, respectively) than PET/CT (sensitivity 91% and specificity 86%). These lesion-based estimates were for 212 lesions that included distant metastases at various sites (most in bone or liver) in 20 patients.\(^{235}\)

**Skeletal Scintigraphy:** Skeletal scintigraphy (bone scan) is an effective method for screening the whole body for bone metastases.\(^{236}\) \(^{99m}\)Tc methylene diphosphonate (MDP), is the most frequently used radionuclide bone scans.\(^{237}\) Because technetium-labeled MDP is taken up by active osteoblasts, \(^{99m}\)Tc planar bone scans detect metastatic tumor deposits in bone through the increased osteoblastic activity they induce. Radionuclide bone scans are relatively insensitive for purely osteolytic lesions found commonly in kidney and thyroid cancers, multiple myeloma, and some lung cancer metastases, but they are highly sensitive to osteoblastic and mixed osteolytic/osteoblastic lesions, such as from prostate and breast cancers. Bone scans have the disadvantages of poor spatial and contrast resolution and lower specificity. SPECT/CT corrects these disadvantages to some degree.

Sensitivity of \(^{99m}\)Tc bone scan is estimated at between 62% and 100%, with the lowest sensitivity seen in patients with predominantly lytic disease. Many benign processes and other entities (eg, trauma fractures, Paget disease) can produce an area of increased radiotracer uptake that mimics a metastatic deposit. Bone scans are not optimal for monitoring response to treatment, because the osteoblast changes induced by cancer metastases can be long-lived. Osteoblastic activity resulting from healing after therapy (ie, flare phenomenon) may misleadingly suggest advancing disease on bone scans. In many patients, further imaging such as plain films or CT is required.
**PET:** PET/CT can help identify bone metastases at an early stage of growth, before host responses of the osteoblasts occur. It has a higher spatial resolution than bone scan, and has a quantitative capability. Because of this, PET can better assess response to therapy. Two currently available PET tracers are 18F-sodium fluoride and 18F-FDG. 18F-sodium fluoride is taken up by osteoblasts and therefore reflective of a reparative response, making fluoride PET scans similar to 99mTc bone scan. 18F-Fluoride becomes incorporated into newly formed bone in increased amounts, reflecting increased turnover. 18F-Sodium fluoride PET has improved lesion detection over bone scans. However, finding additional lesions may not necessarily alter therapy. 18F-FDG PET can detect early malignant bone marrow infiltration because of the early increased glucose metabolism in neoplastic cells.

Unlike 99mTc-MDP bone scans and 18F-sodium fluoride PET bone scans, 18F-FDG PET assesses the metabolic activity of the metastatic tissue directly rather than the bony response to the presence of the metastasis. Therefore, FDG PET can help detect purely osteolytic lesions and marrow infiltration, but may not help identify osteoblastic lesions that have relatively low metabolic activity. Consequently, lesions present on MRI or PET may not be visible on bone scans, and vice versa. These techniques nicely complement each other when mixed lesions are present. A comparative study of 3 modalities in detecting bone metastases found sensitivities of 90% for FDG PET, 82% for whole-body MRI, and 71% for 99mTc bone scans. Similar results have emerged from comparative studies of FDG PET and 99mTc bone scans. FDG PET shows a high number of false-positive lesions, which require follow-up imaging with other modalities. In skull metastases, the high rate of glucose metabolism in the normal areas of brain may obscure tumor metastases. A phenomenon known as “metabolic flare” has been reported in ER-positive tumors, wherein the metastases may show increased FDG intensity on a PET scan. This transient increase in FDG activity is seen after initiation of hormone therapy (typically 7-10 days after treatment initiation) and is believed to be the result of an initial stimulation of tumor growth by estrogen-like agonist effects induced by increased levels of the hormone.

Additional PET tracers are under investigation in cancer imaging. 18F-fluoroestradiol can measure estrogen receptors. Markers of DNA synthesis such as C-11 thymidine and 18F-fluorothymidine can measure cellular proliferation. C-11 acetate can measure lipid biosynthesis, an indication of cellular reproduction.

**SPECT:** SPECT may also be fused with CT (SPECT/CT). Modern SPECT scanners are multifunctional devices that can perform bone scans and SPECT, and can fuse the SPECT and CT datasets to produce hybrid images. SPECT has been reported to be superior to bone scan in detecting vertebral metastases, and its accuracy is enhanced by the fused CT. SPECT/CT is not currently widely available in the United States. SPECT has a higher specificity because of improved anatomic localization.

**Bone Biopsies**

Biopsies of bone metastases are performed to document metastatic disease. Bone is technically challenging to biopsy, because of difficulties in tissue acquisition. Image-guided core needle biopsy is the most common technique for obtaining bone metastasis tissue and is frequently adequate for diagnosing presence or absence of metastatic spread. Bone biopsies can also be performed via standard posterior iliac crest bone marrow trephine/aspiration (non-image guided). Biopsy of bone metastases is technically challenging, with relatively low yields regardless of technique used. Communication among the person performing the biopsy (generally a radiologist if image-guided), the cytologist/pathologist, and the oncology team is critical in obtaining optimal results from bone biopsies.

**Evaluating Response to Treatment of Metastatic Bone Disease**

Bone metastases are challenging when attempting to measure response. Although bone scan, MRI, and CT are effective in detecting bone metastases, changes in response to therapy can be difficult to discern with these modalities. The bone scan can show a “flare” in response to successful therapy. Serial FDG PET has been reported to be helpful in measuring bone metastases response, and changes in FDG uptake have been correlated with clinical response and changes in breast cancer tumor markers. Further study is needed to evaluate the utility and accuracy of PET in this role. The combination of FDG
and fluoride PET for measuring both sclerotic and lytic lesion response may be helpful in monitoring bone response.

No RECIST criteria (either 1.0 or 1.1) measure bone response. Criteria from Union for International Cancer Control and WHO help define what constitutes a response to bone.251

**Summary and NCCN Recommendations**

For imaging patients at risk for bone metastases, the task force stresses adopting a systematic approach based on patient symptoms and the strengths and limitations of the various imaging modalities. Clinicians should consider having a dialogue with the radiologist. Results of imaging studies should always be interpreted within the clinical context of the patient. Understanding the advantages and disadvantages of different bone imaging techniques will assist clinicians in cancer screening, treatment planning, and assessing treatment response. Multiple imaging modalities may be required to confirm the presence and optimally evaluate bone metastases.

Skeletal scintigraphy provides a relatively sensitive and inexpensive evaluation of the entire skeleton in a single imaging examination and is recommended for evaluating patients with multiple sites of bone pain or for the staging of patients at high risk of having metastases. However, over the past decade, a global shortage of the radiotracer 99mTc has emerged because of the shutdown of 2 or more of the 5 reactors in the world that produce the precursor of 99mTc. This has been an intermittent but ongoing problem. Limited evidence exists showing the superiority of one imaging modality over another. A large ongoing study is comparing the diagnostic performance of 18F-fluoride PET/CT scanning to that of 99mTc-MDP bone scanning for detecting bone metastases (ClinicalTrials.gov identifier: NCT00882609). With the currently available data, FDG PET/CT is complementary to bone scintigraphy. The choice of initial screening test used for the detection of bone metastases may depend on the availability, cost, imaging time, and patient preference. MRI is estimated to cost 2 to 3 times as much as 99mTc bone scintigraphy; FDG PET scanning costs 10 times as much.

An example of a scheme of how a patient with cancer with suspected bone metastases might pass through a set of imaging studies is illustrated in Figure 3. Imaging analysis for metastases is focused on the most likely bones of involvement: vertebrae, pelvis, ribs, skull, femur, and humerus. As the figure suggests, patients with suspected bone metastases may be assessed initially with skeletal scintigraphy (99mTc-MDP bone scan).227 Given the high specificity of a negative bone scan, if the bone scan is negative and no symptoms are present, it may be presumed that the patient has no metastatic disease. A positive scintigraph is fol-

allowed by plain film radiography to further localize and characterize the lesion. If radiographs are negative and the patient is still symptomatic or has a suspicious lesion, an MRI or CT scan should be considered.

Monitoring bone metastases can be problematic with any imaging technique, because changes in bone often occur very slowly. 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, plain films and CT scans provide the best information.

**Treatment of Bone Metastases**

**Pharmacologic Options for Patients With Breast Cancer**

**Bisphosphonates:** Randomized controlled trials have clearly shown that long-term bisphosphonate treatment is effective in reducing skeletal morbidity in breast cancer, with fewer SREs, reduced pain and analgesic consumption, and improved QOL. The bisphosphonates are a supportive therapy, yet data show that bisphosphonates may aid in controlling tumor burden and extending life, although the data are mixed. Studies of the effects on life expectancy include those using pamidronate, clodronate, and zoledronic acid. The findings are being further explored.

A pivotal trial showed that pamidronate reduced the frequency of skeletal morbidity in placebo-controlled trials involving patients with breast cancer and bone lesions who were receiving hormone therapy or chemotherapy. The skeletal morbidity rate was 2.4 events per year in the pamidronate arm and 3.7 in the placebo arm (P<.001). The median time to skeletal complication was 12.7 months in the pamidronate group and 7 months in the placebo group (P<.001). In the pamidronate arm, 51% had skeletal complications at up to 24 months on treatment, compared with 64% in the placebo arm (P<.001).

In preclinical testing, zoledronic acid seemed to be a more potent bisphosphonate than pamidronate, and clinically it showed superiority over pamidronate in the treatment of hypercalcemia of malignancy. It has been studied most extensively in breast cancer, prostate cancer, multiple myeloma, and other solid tumors. A randomized, phase III, multicenter trial was conducted to compare zoledronic acid and pamidronate in patients with bone lesions secondary to breast cancer or multiple myeloma, with the objective of determining the safety and efficacy of long-term therapy with these 2 agents. The 13-month core phase of the trial showed that zoledronic acid had an efficacy and safety profile comparable to pamidronate. In a 25-month extension phase, the overall incidence of SREs other than hypercalcemia of malignancy was similar between the zoledronic acid and pamidronate groups. The percentage of patients who required radiotherapy to bone was lower for zoledronic acid (19% vs 24% for pamidronate; P=.037). A comparable median time to first SRE was observed in both groups (376 days for zoledronic acid vs 356 days for pamidronate; P=.151). Zoledronic acid reduced the mean annual incidence of skeletal complications, or skeletal morbidity rate, by 25% compared with pamidronate, with 1.04 events per year for zoledronic acid and 1.39 events per year for pamidronate (P=.084). In the overall patient population, zoledronic acid reduced the risk of developing a skeletal complication by an additional 16% compared with pamidronate, with a risk ratio derived from the multiple-event analysis of 0.841 (P=.030). A randomized trial performed in Japan compared 4 mg of zoledronic acid with placebo every 4 weeks for 1 year in women with breast cancer with at least one osteolytic bone metastasis. The placebo control was used because no intravenous bisphosphonate was approved in Japan for this indication. The trial involving 228 Japanese women found that zoledronic acid reduced the rate of SREs by 39% (P=.027). The absolute reduction in the number of patients having an SRE was 20% (number needed to treat = 5). In addition, bone pain scores were significantly improved within 4 weeks of treatment, and remained modestly reduced for 52 weeks. No serious (grade 3 or 4) toxicities or substantial declines in renal function were observed after one year of treatment. This study corroborates the benefit of zoledronate in reducing SREs seen in previous studies.

Questions remain on how to optimally use the bisphosphonates, including when to initiate therapy, what the ideal interval is between dosing, and how long bisphosphonate therapy should continue. The BISMARK study, which compared standard dosing of zoledronic acid at 4 mg intravenously every 3 to 4 weeks versus a marker-directed schedule based
on updated levels of urinary N-terminal telopeptide (uNTx). The study recruited 289 patients of the 1500 planned enrollment and was stopped early. Therefore, the results are underpowered to show noninferiority in SRE outcome between the treatment strategies. The limited results suggest that the adjustment of zoledronic acid schedule based on NTx values alone may not represent optimal management. Ongoing clinical trials will help identify optimal dosing schedules, duration, and the role of other novel agents in the treatment of bone metastases. The randomized phase III ZOOM trial assessed the safety and efficacy of switching to quarterly zoledronic acid versus continuing with monthly in patients (n=425) with bone metastases from breast cancer who received prior zoledronic acid treatment. Safety analyses showed that zoledronic acid was well tolerated in the long term, and renal adverse events were seen in similar proportions of patients in both arms. This study was underpowered to confirm noninferiority between the arms, although rates of SREs were similar. Similarly, the ongoing OPTIMIZE 2 trial is studying patients with breast cancer with bone metastases who have received prior monthly zoledronic acid. OPTIMIZE 2 patients are randomized in a double-blind fashion to continue monthly dosing for an additional year versus changing dosing intervals to every 3 months (ClinicalTrials.gov identifier: NCT00320710). OPTIMIZE 2 has fully enrolled and follow-up is ongoing. The CALGB 70604 trial has completed accrual and is studying patients with metastatic bone disease from breast cancer, prostate cancer, or multi-

### Table 3: Comparison of Outcome of Bone-Modifying Treatments in Patients With Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment vs Control</th>
<th>Number of Patients</th>
<th>Median Time to First SRE Treatment vs Control (mo)</th>
<th>% of Patients With SRE Treatment vs Control</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hortobagyi et al 261</td>
<td>Pamidronate, 90 mg every 3–4 wk vs placebo</td>
<td>380</td>
<td>13.1 vs 7.0</td>
<td>43 vs 56 (at the end of 1 y)</td>
<td>The analysis included hypercalcemia of malignancy</td>
</tr>
<tr>
<td>Theriault et al 262</td>
<td>Pamidronate, 90 mg every 3–4 wk vs placebo</td>
<td>371</td>
<td>10.4 vs 6.9</td>
<td>56 vs 67 (at the end of 2 y)</td>
<td>The analysis included hypercalcemia of malignancy</td>
</tr>
<tr>
<td>Rosen et al 263</td>
<td>Zoledronic acid, 4 mg every 3–4 wk vs Pamidronate, 90 mg every 3–4 wk</td>
<td>524 (received chemotherapy)</td>
<td>11.6 vs 12.2</td>
<td>46 vs 49 (at the end of 2 y in the combined group analysis)</td>
<td>The analysis excluded hypercalcemia of malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>606 (received hormone therapy)</td>
<td>13.8 vs 12.3</td>
<td></td>
<td>In initially patients randomized to zoledronic acid were randomized to receive 4 or 8 mg; however, because of renal safety concerns, the 8-mg dose was reduced to 4 mg</td>
</tr>
<tr>
<td>Kohno et al 260</td>
<td>Zoledronic acid, 4 mg every 3–4 wk vs placebo</td>
<td>227</td>
<td>NR vs 12.1</td>
<td>29.8 vs 49.6 (at the end of 1 y)</td>
<td>The analysis excluded hypercalcemia of malignancy</td>
</tr>
<tr>
<td>Stopeck et al 264</td>
<td>Denosumab, 120 mg SQ every 4 wk vs Zoledronic acid, 4 mg every 3–4 wk</td>
<td>2046</td>
<td>NR vs 26.4</td>
<td>40 vs 50 (at the end of 2 y)</td>
<td>The analysis excluded hypercalcemia of malignancy</td>
</tr>
</tbody>
</table>

In some studies hypercalcemia was reported separately from the primary SRE analysis. Abbreviations: NR, not reached; SRE, skeletal-related event; SQ, subcutaneously.
ple myeloma. Patients were randomized to zoledronic acid, 4 mg every 4 weeks versus every 12 weeks, and the study is investigating the rate of SREs between the groups over 2 years (ClinicalTrials.gov identifier: NCT00869206).

Despite optimal bisphosphonate therapy, approximately 40% of patients with cancer with bone metastases still develop SREs while on bisphosphonate therapy.260,262 The introduction of antiresorptive agents has significantly increased the median time to first SRE over the years (Table 3).

Concerning toxicities are also associated with antiresorptive agents, such as ONJ and hypocalcemia. Intravenous infusion of zoledronic acid can be associated with an acute-phase reaction, including bone pain, fever, and chills in up to 30% of patients after their first infusion, and zoledronic acid in particular confers a risk of renal toxicity that is dose-dependent and infusion time-dependent (See “Adverse Effects and Safety Considerations While Using Antiresorptive Agents,” page S-34).

Denosumab: In a phase II study of patients with metastatic bone disease, denosumab normalized the uNTx levels in a significantly greater proportion of patients than those who continued with an intravenous bisphosphonate.265 Biochemical markers of bone metabolism are not established means for monitoring bone metastases or antiresorptive therapy, and are in need of further investigation. In this phase II study, fewer patients receiving denosumab experienced on-study SREs than those receiving intravenous bisphosphonates.

In a phase III trial, patients (n=2046) with metastatic breast cancer and radiologic evidence of at least one bone metastasis were randomized to receive either subcutaneous denosumab at 120 mg and intravenous placebo (n=1026) or intravenous zoledronic acid at 4 mg (with adjustment for creatinine clearance) and subcutaneous placebo (n=1020) every 4 weeks.115 The primary end point of the study powered to detect noninferiority of denosumab versus zoledronic acid was time to first SRE. Secondary end points included time to first on-study SRE (superiority test) and time to first and subsequent on-study SRE (multiple-event analysis). Denosumab delayed the time to first on-study SRE by 18% compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–0.95; P=.001 for noninferiority, P=.01 for superiority). Denosumab also reduced the risk of subsequent SREs by 23% (risk ratio, 0.77; 95% CI, 0.66–0.89; P=.001). OS and disease progression were similar between the groups.115 The main adverse effects associated with denosumab were fatigue, asthenia, hypophosphatemia, and nausea115 (see “Adverse Effects and Safety Considerations While Using Antiresorptive Agents,” S-34).

Summary and NCCN Recommendations: Bisphosphonates and denosumab have shown clinical benefits in patients with bone metastases from breast cancer. The NCCN Task Force agrees with the ASCO guidelines recommending that therapy with an antiresorptive agent be initiated in the presence of a documented metastatic bone lesion.266 Pamidronate, zoledronic acid, and denosumab been shown to be efficacious in reducing/delaying onset of SREs in patients with metastatic bone disease. Of the 3 FDA-approved antiresorptive agents for the management of metastatic bone disease (denosumab, pamidronate, and zoledronic acid), zoledronic acid is indicated for the greater range of tumors; however, denosumab has shown improved efficacy in the tumors for which it carries a label indication. Clinical judgment must be used in determining which antiresorptive agent is appropriate for the patient under consideration.

Zoledronic acid at 4 mg or pamidronate at 90 mg are given intravenously every 3 to 4 weeks.267 Zoledronic acid and pamidronate are not recommended for creatinine clearance less than 30 mL/min. Denosumab at 120 mg is given subcutaneously every 4 weeks.262 Although renal monitoring is not required, denosumab is not recommended in patients with creatinine clearance less than 30 mL/min. Even in patients with normal renal function, hypocalcemia is higher with denosumab than with zoledronic acid, and all patients on denosumab should be treated with vitamin D and calcium, and undergo periodic monitoring of serum calcium levels. Before therapy with an antiresorptive agent is initiated, the panel recommends evaluation of oral health and assessment of vitamin D and nutritional status.

The results of the phase III clinical trials examining dosing intervals are eagerly awaited. No published prospective clinical trials have compared different durations of therapy with an antiresorptive agent. The longest duration of study in the phase III clinical trials of antiresorptive agents is less
than 3 years. The potential additional benefit from continuing antiresorptive agents must be weighed against the potential toxicities of long-term administration of these drugs. For patients with breast cancer, the NCCN Task Force agrees with the ASCO guidelines recommending that antiresorptive therapy, once initiated, be continued until evidence is seen of substantial decline in the patient’s general performance status.266

Pharmacologic Options for Patients With Prostate Cancer
Prostate cancer commonly metastasizes to bone,269 and almost 90% of patients with advanced prostate cancer have radiographic evidence of bone metastases.270–273

Morbidity from complications of bone metastases, such as pathologic fractures, spinal cord compression, and pain, greatly impairs the QOL of patients with metastatic prostate cancer.274 Bone pain has negative impact on prognosis.275–277 ADT is the initial treatment for metastatic prostate cancer. A significant improvement in pain relief, a decline in PSA levels, and an improvement in QOL are seen with ADT. Unfortunately, in most cases the disease relapses after a median response of approximately 2 years, turning into castration-resistant prostate cancer. Within the past decade the outlook has changed considerably. Docetaxel-based chemotherapy is established as a well-tolerated treatment with statistically significant survival benefits compared with mitoxantrone.278 Several classes of drugs have been added to the treatment armamentarium, including immunotherapy agents, androgen receptor–targeting drugs, novel antiresorptive agents, and radiopharmaceuticals. Many of these drugs approved for improvement in OS have also shown direct effects on reduction of SREs.

Chemotherapy: For patients with metastatic prostate cancer, first-line therapy is systemic chemotherapy with docetaxel. Docetaxel-based therapy has shown improved OS in 2 randomized phase III trials.270,278 Occurrence of SREs was not an end point in these studies; however, QOL was found to be significantly improved in the docetaxel arm, with pain reduction in 35% of patients versus 22% of those in the placebo arm. Recently, cabazitaxel, a microtubule-targeting drug, was shown to provide OS and QOL improvements after docetaxel therapy.271 The findings from the phase III TROPIC trial established cabazitaxel as the first agent to prolong survival after docetaxel-based therapy, with a 30% reduction in death over mitoxantrone.271 Interestingly, the pain response rate was no different between the groups. No SRE assessment was performed in this trial.

Immunotherapy: Sipuleucel-T is an active immunotherapy vaccine, consisting of autologous peripheral blood mononuclear cells, including antigen-presenting cells that have been activated ex vivo with a recombinant fusion protein (PA2024). This protein consists of a prostate antigen that is fused to a granulocyte-macrophage colony-stimulating factor, which acts as an immune cell activator. Sipuleucel-T is FDA-approved for the treatment of metastatic castration-resistant prostate cancer in men with minimal or no symptoms. A recent meta-analysis of 3 phase III trials279–281 confirmed the findings that treatment with sipuleucel-T leads to a significant improvement in OS for men with metastatic castration-resistant prostate cancer.282 By contrast, the time to disease progression did not differ significantly between treatment arms.276

Hormone Therapy: Abiraterone acetate, a CYP inhibitor was recently FDA-approved for patients with metastatic castration-resistant prostate cancer. The COU-AA-301 trial assessing abiraterone acetate after therapy with docetaxel showed improved pain palliation compared with placebo (in 45.0% vs 28.8%), and time to first SRE was 25.0 months with abiraterone acetate versus 20.3 months with placebo (P=.0006).283,284 In the final analysis, abiraterone acetate significantly prolonged OS compared with placebo in patients with metastatic castration-resistant prostate cancer who progressed after docetaxel treatment (15.8 vs 11.2 months; HR, 0.74; 95% CI, 0.64–0.86; P<.0001).272 Time to radiographic progression, PSA decline, and pain palliation were also improved with abiraterone acetate.272,284

Interestingly, abiraterone acetate is also effective in chemotherapy-naïve patients. The COU-AA-302 study results revealed statistically better progression-free survival and a trend toward improved OS rates in chemotherapy-naïve patients treated with abiraterone versus placebo.285 Based on these results, the study was terminated early and unblinded, a decision made by the Independent Data Monitoring Committee. The FDA has since approved use of abiraterone acetate in chemotherapy-naïve patients with castration-resistant prostate cancer.

Enzalutamide, a potent androgen inhibitor, recently received FDA approval for the treatment of...
patients with metastatic castration-resistant prostate cancer who have previously received docetaxel therapy. The phase III AFFIRM trial showed higher survival rates with enzalutamide compared with placebo (18.4 vs 13.6 months).\textsuperscript{273} In addition, the time to the first SRE was also significantly longer with enzalutamide (16.7 vs 13.3 months; HR, 0.69; \textit{P}<.001). A randomized, double-blind, placebo-controlled phase III study (PREVAIL) is evaluating the effect of enzalutamide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer. The study was closed to accrual in March 2012 and the results are awaited (ClinicalTrials.gov identifier: NCT01212991).

Taken together, these data show that the new-generation hormone therapy agents that are effective in improving the OS of patients with castration-resistant prostate cancer also reduce SREs.

**Bone-Targeted Therapies:** Several drugs targeting bone turnover have been approved because of their ability to reduce bone complications. Patients with bone metastases from prostate cancer and high levels of bone markers, such as uNTx levels, have an increased risk of SREs, time to a first SRE, disease progression, and death.\textsuperscript{286,287}

**Bisphosphonates:** Bisphosphonates are effective in reducing bone complications in patients with osteolytic bone metastases from a variety of solid tumors. Because prostate cancer is primarily osteoblastic, it was initially thought that bisphosphonates may not be as effective in this disease. However, studies have shown that bone resorption in metastatic prostate cancer is very high, reflecting substantial osteoclastic activity. Therefore, a biologic rationale exists for the use of bisphosphonates in prostate cancer.

Zoledronic acid is the only bisphosphonate with proven clinical benefit in reducing skeletal complications in patients with hormone-refractory prostate cancer. In a double-blind phase III trial, patients with hormone-refractory disease (rising PSA despite medical or surgical castration) and a history of bone metastases were randomized to zoledronic acid at 4 mg (n=214), zoledronic acid at 8 mg (n=221), or placebo (n=208) every 3 weeks for 15 months.\textsuperscript{288} The primary end point was time to occurrence of SREs. Risk of renal impairment was elevated in patients treated with 8 mg of zoledronic acid, and therefore the dose was reduced to 4 mg. Patients on placebo had significantly more SREs than those on zoledronic acid (44.2% vs 33.2%). Subsequently, data reported on 122 patients who completed a total of 24 months on study showed that fewer patients treated with zoledronic acid developed skeletal complications (38% vs 49% for the placebo group).\textsuperscript{289} Compared with placebo, 4 mg of zoledronic acid reduced the ongoing risk of SREs by 36% (risk ratio, 0.64; 95% CI, 0.485–0.845; \textit{P}=.002).\textsuperscript{261} Overall, a decrease in fracture, spinal cord compression, antineoplastic therapy, and need for radiation and surgery was seen in patients receiving zoledronic acid compared with placebo. The most common adverse events reported in at least 5% more patients in the zoledronic acid group were fatigue, anemia, myalgia, fever, and lower-limb edema. Although therapy with bisphosphonates is effective at preventing SREs in men with castration-resistant prostate cancer, the use of bisphosphonates in men with castration-sensitive disease remains an open question.

**Denosumab:** A phase III trial randomized 1904 patients with metastatic castration-resistant prostate cancer to receive either denosumab or zoledronic acid.\textsuperscript{289} Eligible patients had evidence of at least one bone metastasis and documented failure of at least one hormonal therapy. As in the breast cancer trial, patients were required to have a creatinine clearance greater than 30 mL/min to be eligible for randomization to the zoledronic acid arm. All patients were strongly encouraged to take vitamin D and calcium supplementation. The primary end point of the study powered to detect noninferiority of denosumab versus zoledronic acid was time to first SRE. The median time to first on-study SRE was 20.7 months for patients on denosumab (95% CI, 18.8–24.9) versus 17.1 months for those on zoledronic acid (95% CI, 15.0–19.4), with an HR of 0.82 (95% CI, 0.71–0.95; \textit{P}=.002 for noninferiority and \textit{P}=.008 for superiority).\textsuperscript{289} A delay in time to first on-study SRE was 18% with denosumab compared with zoledronic acid, identical to the results from the trial in metastatic breast cancer. At week 13, the decrease in uNTx level was significantly greater in the denosumab group (median decrease of 84% in the denosumab group vs 69% in the zoledronic acid group; \textit{P}=.0001). As in the phase III study in patients with breast cancer, denosumab was superior to zoledronic acid for preventing skeletal complications from metastasis. OS and disease progression were not significantly different between the treatment groups. Occur-
rence of adverse events and serious adverse events were similar between the groups. Hypocalcemia was more common in the denosumab group (13% in the denosumab group vs 6% in the zoledronic acid group; P= .0001). The cumulative rates of ONJ between the groups were not statistically significant, at 1% (n=12) in the zoledronic acid group versus 2% (n=22) in the denosumab group. Adverse events associated with acute-phase reactions occurred in 8% of patients on denosumab and 18% of patients on zoledronic acid. Adverse events related to renal impairment were similar between the groups, at 15% in the denosumab group and 16% in the zoledronic acid group. However, the zoledronic acid group required more frequent dose adjustment and withholding for renal dysfunction.289

**Radiopharmaceuticals:** Radium-223 (223Ra) is an α-particle emitter with high affinity for the bone matrix. 223Ra and calcium belong to the same group of alkaline earth elements in the periodic table, owing to their similar chemical properties and affinities. The difference between 223Ra compared with other isotopes, such as samarium-153 or strontium-89, is that it penetrates a very small radius; therefore, the risk of having bone marrow suppression is a lot less with 223Ra.

223Ra was studied in a large phase III trial (AL-SYMPCA) in men with castration-resistant disease with bone metastases, who either previously received docetaxel or were ineligible to receive docetaxel. The trial showed improvement in OS compared with placebo (median OS, 14 vs 11.2 months; P=.00185).290 Time to first SRE was also delayed (median time to SRE, 13.6 vs 8.4 months; P=.00046).290 Spinal cord compression and pathologic bone fractures were less frequent in the 223Ra-treated patients compared with those treated with placebo. The effect of 223Ra on QOL and in pain palliation has not been reported. Grade 2 or 3 hematologic adverse events were similar in both groups studied. This is the first phase III trial evaluating a radiopharmaceutical and demonstrating an OS advantage with 223Ra treatment in men with symptomatic castration-resistant prostate cancer with bone metastases.290 The FDA has approved the use of 223Ra in men with symptomatic metastatic castration-resistant prostate cancer that has spread to the bone but not to other organs.

**Other Therapeutics Targeting the Bone in Clinical Development:** Dasatinib was assessed in a phase II study in 48 chemotherapy-naive patients with metastatic castration-resistant prostate cancer.291 Only 17% of the patients did not have disease progression at 24 weeks. However, uNTx levels were reduced by 40% or more in 51% of patients, and bone alkaline phosphatase was decreased in 59% of patients.292 A phase II study of combination dasatinib and docetaxel therapy showed a high response rate in men with castration-resistant prostate cancer. The study included 46 patients, some of whom were previously treated with docetaxel.292 According to the results, a 50% decline in PSA was seen in 26 of 46 patients (57%); 60% of the patients with measurable disease had a partial response; 30% had disappearance of a lesion on bone scan; and uNTx levels decreased in 87% of patients.292 A phase III trial evaluating docetaxel alone or in combination with dasatinib was recently reported and did not meet its primary end point of OS (ClinicalTrials.gov identifier: NCT00744497).

Cabozantinib is a vasculature-disrupting agent that inhibits tumor angiogenesis and metastasis.293 A phase II trial of patients with castration-resistant prostate cancer treated with cabozantinib showed impressive improvements in pain palliation and resolution of lesions on bone scan.294 The results of a phase II nonrandomized expansion cohort study reported high rates of bone scan response, pain relief, and reductions in bone turnover markers with cabozantinib in patients previously treated with docetaxel.295 A phase III trial (COMET-2) comparing cabozantinib and mitoxantrone plus prednisone is ongoing. The primary end point of this trial is pain response.

**Summary and NCCN Recommendations:** In patients with metastatic castration-resistant prostate cancer, a series of recent phase III studies showed that agents such as cabazitaxel, abiraterone, enzalutamide, sipuleucel-T, and 223Ra improve OS and inhibit disease progression to the bone. With a better understanding of the role of approved and other novel bone-targeted agents in treatment-related bone loss, prevention and treatment of metastases, and antitumor effects, the role they play will likely expand in the management of advanced prostate cancer. No proven role of bone-targeted therapy exists in hormone-naïve patients diagnosed with advanced prostate cancer, and currently hormone therapy adequately controls the underlying disease in this setting.

In patients with castration-resistant prostate cancer, the main risk factor for skeletal complications is the presence of bone metastases. Denosum-
ab and zoledronic acid have been shown to prevent disease-related skeletal complications, including fracture, spinal cord compression, or the need for surgery or radiotherapy to bone. Men with castration-resistant prostate cancer who have bone metastases and are at high risk for SREs should be considered for bone-targeted therapy with zoledronic acid or denosumab. Given the largely osteoblastic nature of prostate cancer metastases that may affect calcium homeostasis and create a low-normal serum calcium level, supplemental calcium and correction of vitamin D deficiency are key to lowering the risk for potential hypocalcemia resulting from these agents.

As with other tumors, insufficient data exist to guide the choice, dose, and route of administration and duration of bone-targeted therapy in patients with prostate cancer. Denosumab has demonstrated benefits over zoledronic acid in preventing or delaying SREs; however, from an economic perspective it is very costly. According to the NCCN Guidelines for Prostate Cancer, “choice of agent may depend on underlying comorbidities, whether the patient has been treated with zoledronic acid previously, logistics, and/or cost considerations.” The NCCN Task Force agrees with this.

Zoledronic acid, 4 mg, is given intravenously every 3 to 4 weeks. The dose is based on the serum creatinine obtained just before each dose and must be adjusted for impaired renal function. Zoledronic acid is not recommended for creatinine clearance less than 30 mL/min. Denosumab, 120 mg, is given subcutaneously every 4 weeks. Although renal monitoring is not required, similar to zoledronic acid, denosumab is not recommended in patients with creatinine clearance less than 30 mL/min. Even in patients with normal renal function, hypocalcemia is seen twice as often with denosumab than zoledronic acid, and all patients on denosumab should be treated with vitamin D and calcium, with periodic monitoring of serum calcium levels.

The optimal duration of therapy with either denosumab or zoledronic acid remains uncertain. In the zoledronic trial, patients were treated up to 2 years; however, the denosumab trial had no maximum treatment duration, so patients were treated for longer periods. If patients tolerate the drugs without any issues and seem to have a clinical benefit, it may be reasonable to continue therapy.

Antiresorptive Agents for Palliation of Bone Pain

Although antiresorptive agents are primarily used to reduce overall skeletal events, clinical trials have established that bisphosphonates have an analgesic effect on patients with metastatic bone pain from a variety of tumors. Because of differences in patient populations and methods for assessing bone pain, direct comparison of bisphosphonates to determine their relative effects on bone pain across studies is difficult. Data from randomized trials indicate that ibandronate (6 mg intravenously and 50 mg orally) reduces pain and maintains it below baseline levels compared with placebo in patients with breast cancer. Short-term clodronate has also been shown to be effective in reducing pain scores in patients with advanced cancer. A small study comparing the efficacy and safety of zoledronic acid administered in the community versus the hospital setting in patients with breast cancer found that zoledronic acid significantly improved composite pain scores and overall QOL compared with baseline. A phase III study of patients with breast cancer and multiple myeloma showed that bone pain relief below baseline was obtained with 1 year of treatment with 4 mg of zoledronic acid and 90 mg of pamidronate.

Denosumab has also shown improved pain prevention and comparable pain palliation. Patient-reported pain interference with daily functioning was evaluated using data from a phase III trial comparing denosumab with zoledronic acid in women with advanced breast cancer and bone metastases. Results showed that time to improvement in pain interference with activity tended to occur more rapidly with denosumab than with zoledronic acid (a median of 70 vs 86 days; P=.09). It was noted that fewer patients treated with denosumab shifted to strong opioid analgesic use.

Surgery and Radiation

Localized therapies, including radiation and surgery, can be used to prevent an impending skeletal event and provide pain palliation.

Radiation Treatment: Radiotherapy is commonly used in the management of bone metastases, both for pain relief and prevention of morbidity and disease progression. Radiotherapy has been shown to provide responses rates of 60% to 70%. Complete pain relief may occur in 20% to 30% of patients receiving radiotherapy. In many patients, the effects may
not be felt for several weeks after the start of treatment, and the duration of relief may last only 3 to 4 months. A wide range of radiotherapeutic options also exist for pain that recurs after external-beam radiation therapy (EBRT) has been given for bone metastases. Among these options is a second course of EBRT to the same localized site. Additionally, using a different mode of radiotherapy delivery, such as stereotactic body radiotherapy (SBRT), could improve the results of the primary treatment or repeat treatment of metastatic spinal lesions.

**External-Beam Radiation Therapy:** EBRT is widely used for patients with cancer who present with localized bone pain. Debate exists over the optimal treatment schedule: single-fraction versus multiple-fraction EBRT. A systematic review of published trials shows no difference between single-fraction and multiple-fraction EBRT in terms of efficacy and toxicity, although a slightly higher retreatment rate has been seen with single-fraction treatment. The Radiation Therapy and Oncology Group (RTOG) conducted one of the largest trials in the United States studying effects of a single fraction versus multiple fractions of EBRT in treating bone metastases in patients with breast and prostate cancers. Patients (n=898) were randomized to a single 8-Gy fraction or 30 Gy given in 10 fractions. No significant difference in response rates were seen between the arms, although a significantly higher retreatment rate was seen the single-fraction arm. The RTOG trial showed more acute toxicity (grades 2–4) in the multiple-fraction arm compared with the single-fraction arm. The higher retreatment rate with single-fraction treatment may be attributed to the bias that giving additional radiation doses may help patients who have had no relief from a single fraction of radiation. Results of the updated meta-analyses of 25 randomized palliative radiotherapy trials comparing single versus multiple fractions show that both provided equal pain relief; however, significantly higher retreatment rates occurred in those receiving single fractions. Overall and complete response rates were similar in both intention-to-treat and assessable patients receiving either single or multiple fractions.

The ASTRO task force compared studies with several dosing schema, including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8-Gy fraction. Although a slightly higher retreatment rate was found with single-fraction radiation; they found equivalency in single versus multiple fractions in terms of pain relief in previously unirradiated patients with painful bone metastases. The ASTRO guidelines on palliative radiotherapy for bone metastasis state that “the single fraction treatment approach optimizes patient and caregiver convenience.”

In addition, a recent study comparing single versus multiple fractions for palliation of vertebral bone metastases concluded that, compared with multiple-fraction therapy, single-fraction radiation provided equivalent efficacy, comparable narcotic use, less toxicity, and a more convenient regimen. In patients with advanced cancer, QOL is the primary outcome of interest over other end points, such as survival. In a recent study, the QOL was assessed using a new bone metastasis–specific EORTC QLQ-BM22 tool that is able to differentiate patients who experience response to treatment from those who do not. The study reported that patients who experience pain relief from palliative radiotherapy for bone metastases also have improved QOL.

A cost-utility analysis performed in the Netherlands compared 2-year quality-adjusted life expectancies and 12-week societal costs. Total societal costs for radiotherapy (including retreatments, nonmedical costs, and nonradiotherapy costs) were estimated at $4700 and $6453 for single and multiple fractions, respectively. Despite multiple studies indicating no difference in response rate, duration of response, use of pain medication, side effects, or QOL, radiation oncologists in the United States seem to be reluctant to deliver single-fraction radiation for uncomplicated bone metastases.

Pain flare is defined as a temporary worsening of bone pain in the irradiated metastatic site within a week of radiotherapy. Pain flare occurs in more than one-third of patients receiving EBRT. A study reported a significant difference in pain flares based on the primary cancer site. Twice as many patients with primary breast cancer experienced a pain flare compared with those having primary prostate or lung cancers (52% in breast cancer, 25% in prostate cancer, 23% in lung cancer; P=.0227). No significant difference was seen between pain flare incidence rates for patients treated with a single fraction or multiple fractions. A single dose of dexamethasone, administered immediately (first 2 days) after radiotherapy, was
shown to reduce the incidence of pain flare. Therefore, dexamethasone may be used prophylactically to reduce radiotherapy-induced pain flare. Randomized studies are needed to confirm this finding.

**Stereotactic Body Radiation Therapy:** SBRT is a technology that delivers targeted high-dose radiation. It was initially developed for targeting lung lesions, and is now being used to treat spine metastases. Although conventional radiotherapy of spinal metastatic tumors is useful for palliation, its effectiveness is limited by spinal cord tolerance. In patients who harbor spinal metastases not causing cord compression, stereotactic radiation can be used to overcome some of the dose limitation associated with conventional radiotherapy, or in patients who have a good prognosis such that more-aggressive treatment may be warranted. This technique is characterized by high-dose radiation delivered precisely to an extracranial target in 1 to 5 fractions. Response rates are approximately 90% and duration is 13 months, with little to no long-term toxicity, and retreatment rates range from 0% to 15%. SBRT is a relatively technologically sophisticated and costly technique that allows better sparing of adjacent critical normal structures. The ASTRO guidelines clearly state that SBRT should only be used within available clinical trials and should not be the primary treatment of vertebral bone lesions causing spinal cord compression.

**Surgical Treatment:** Surgical management of bone metastases is performed to relieve pain, provide stabilization, and prevent impending fracture or spinal cord compression. In some situations, surgery provides a greater likelihood of return to ambulatory status than radiation alone.

Although surgical treatment of pathologic fractures is often straightforward, treatment of patients with impending pathologic fractures is preferable. 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. The widespread use of bisphosphonate therapy has resulted in a decrease in the incidence of fracture from bone metastases. Identification of bones at risk remains a “moving target” in the face of better anticancer therapies.

Surgeons identify lesions at high risk for fracture based on general criteria: lytic lesions greater than 2.5 cm in diameter, lesions encompassing more than 50% of the bone diameter, or the presence of lesser trochanter avulsion. 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 EBRT. It is important to verify that the lesion is clearly the source of pain. These general guidelines must be interpreted in the specific clinical context. Fracture stabilization must be preceded by an assessment of metastatic disease in other bones, which could compromise rehabilitation. When considering stabilization of a femoral fracture, a long bone survey or a bone scan within 2 to 3 months is recommended to detect other sites of disease that may relate to weight-bearing. Differentiating pathologic fractures from traumatic fractures is very important. Preoperative assessment should include estimation of life expectancy, mental status, mobility status, pain level, metabolic status, skin condition, and nutritional status.

From a technical standpoint, one of the easiest bones to stabilize is the proximal femoral shaft, whereas stabilization is more challenging in the pelvis-acetabulum, spine, and periarticular areas. For a periarticular fracture, prosthetic replacement confers fairly predictable pain relief and a return to ambulatory status. Procedures that are applicable to nonmetastatic traumatic fractures often do not apply in the setting of pathologic fractures. For example, a sliding hip screw is commonly used in patients with intertrochanteric osteoporotic fractures. However, these devices are not effective in patients with pathologic fractures, because of the lack of bone healing, particularly with planned subsequent bone radiation.

Fractures within the femoral diaphysis can be stabilized using intramedullary nailing. Some of the interlocking capabilities of plates and nails have improved over the past 3 years with new locking plate technology. Humeral shaft metastases are often treated with locked intramedullary nailing or, more recently, an inflatable nail, with excellent pain relief and regained use of the extremity in several days. A prospective study found that for treatment of periarticular metastases, locking-plate technology provides durable fixation and good pain relief. Insertion of intramedullary nails is a relatively straightforward procedure that requires general or regional anesthesia and a hospital stay of approximately 2 days. Case series of patients treated with intramedullary nailing have reported good outcomes, with complete pain relief and...
Stabilization of acetabular disease is technically challenging but is generally performed with a variation of hip replacement. Marco et al reported on a case series of 55 patients who were treated with curettage of the tumor, pros torus cup, cement, and pin or screw fixation. Although 76% of patients had a decrease in narcotic use and half of the nonambulatory patients regained the ability to walk, this procedure was associated with a 22% complication rate. Saddle prosthesis is another option; a case series of 20 patients showed a similar improvement in analgesia, independence, and ambulation. Again, however, the complication rate was high at 20%. This high morbidity underscores the importance of patient selection for extensive surgery.

**Additional Minimally Invasive Techniques:** Although surgery may result in improved outcomes, it can also be associated with high morbidity and complication rates, especially in patients with numerous cancer-related comorbidities. A variety of minimally invasive techniques are available, including radiofrequency ablation (RFA); percutaneous osteoplasty, also referred to as cementoplasty; percutaneous vertebroplasty; and kyphoplasty.

RFA uses thermal energy to destroy tumor cells and has been used to treat painful bony metastases. Goetz et al reported on a multicenter prospective study of RFA in which 43 patients with painful bone metastases, most of whom had undergone prior radiotherapy, had significant pain relief and reduction in opioid use with minimal side effects.

Percutaneous vertebroplasty and kyphoplasty describe the injection of surgical cement, usually polymethylmethacrylate (PMMA), into fractured vertebral bodies. These procedures give relief in patients with vertebral body compression fractures that do not cause neurologic deficits but severely compromise QOL largely because of intractable pain. With percutaneous vertebroplasty, PMMA is injected percutaneously into a vertebral body under radiologic guidance to provide pain relief and strengthen bone in painful vertebral body compression fractures. A retrospective study evaluated individuals (n=19) with primary breast, prostate, lung, and renal cancers who underwent percutaneous vertebroplasty procedures. Of these, 53% were treated for solitary lesions, 16% underwent injections at 2 levels, and 31% underwent cement injection at 3 levels. Most individuals (84%) reported short- and long-term symptomatic improvements. In another study of 51 patients, percutaneous vertebroplasty provided effective analgesia in patients experiencing pain related to malignant spinal tumors with epidural extension, and was associated with a relatively low complication rate. A systematic review of the safety and efficacy of percutaneous vertebroplasty in malignancy indicated pain reduction between 47% and 87%, with a significant (up to 2%) risk of serious complications.

Kyphoplasty uses a bone tamp that is inflated before the procedure to create a space for PMMA injection. Kyphoplasty may result in an increase in vertebral height, which may provide a biomechanical advantage over vertebroplasty. This technique is effective for reducing pain associated with both metastatic disease and osteoporosis, although the mechanism of the effect remains unclear. Although this technique is growing in popularity, outcomes in the published literature regarding treatment of metastatic disease are still minimal. In a case series of 97 procedures in 56 patients, a total of 84% of patients had marked or complete pain relief. These results seem to be comparable to those found in the larger volume of literature on kyphoplasty as a treatment of osteoporosis-related vertebral fractures. A retrospective review of clinical outcome data for 48 patients with multiple spinal metastases treated with kyphoplasty, concluded that kyphoplasty is effective in stabilizing pathologic vertebral fractures caused by metastatic disease, leading to a statistically significant reduction in pain, improvement in function, and prevention of further deformity of the spine.

Cementoplasty is the percutaneous injection of PMMA into a metastatic lesion to palliate pain. This technique is similar to vertebroplasty, the difference being that it is performed in areas other than the spine using 3-dimensional imaging, most commonly CT scan. This technique is most suited to the pelvis.

Image-guided cryoa blation is a relatively new minimally invasive technique. Similar to RFA, the metastatic lesions are accessed percutaneously. Cryo-probes are introduced under anesthesia. As the argon gas released from the probes rapidly expands, it produces rapid cooling with temperatures close to \(-100^\circ\text{C}\), leading to intracellular ice ball formation,
dehydration, and cell death. Callstrom et al\textsuperscript{335} reported on 14 patients with bone metastases treated with image-guided cryoablation, noting improvement in pain, decrease in pain interference with activities of daily living, and marked reductions in narcotic use.

Along with the increasing life expectancy of patients with cancer, the prevalence of thoracolumbar spine metastases has also increased over the past 2 decades.\textsuperscript{336} For the management of symptomatic thoracolumbar spine metastases, minimally invasive decompression and stabilization have been shown to improve pain and decrease neurologic deficit, with a lower overall morbidity rate than that associated with the conventional techniques.\textsuperscript{337}

**Summary and NCCN Recommendations:** Advances in surgery allow for the use of several techniques for treatment of bone pain from metastases. An urgent need exists to improve the prediction of fracture risk for patients with cancer with bone metastases. Recently a very small study involving 10 patients showed that quantitative CT-based computer models can improve prediction of bone strength compared with prediction by clinical experts.\textsuperscript{338} The key to optimal surgical management remains the identification of patients who have impending fractures and referring them for stabilization. Consultation between other members of the multidisciplinary team and an orthopedic specialist is recommended to determine optimal management strategy.

According to the task force, single-fraction radiotherapy should be considered for most patients, especially those with limited longevity. SBRT must be administered in a clinical trial setting. Prophylactic interventional surgery may be considered in selected patients with impending long bone fractures. Radiation can generally be given 7 to 10 days after long bone stabilization with intramedullary nails, and 2 to 3 weeks after open plating or prosthetic replacements.

**Adverse Effects and Safety Considerations While Using Antiresorptive Agents**

Antiresorptive agents, including bisphosphonates and denosumab, are generally well tolerated, and pivotal clinical trials have reported a relatively low risk of serious adverse effects. Postmarketing experience with these agents has raised additional cautionary notes regarding rare potential side effects.

**Renal Toxicity**

Bisphosphonates are cleared renally and can cause renal toxicity from increased serum creatinine. The risk for bisphosphonate-associated renal insufficiency seems to be related to dose, infusion rate, and hydration. Among the intravenous bisphosphonates, renal toxicity seems to be more common with zoledronic acid versus pamidronate.\textsuperscript{266} Intravenous bisphosphonates are generally not recommended in patients with creatinine clearance less than 30 mL/min, because they can increase serum creatinine and may rarely cause acute renal failure.\textsuperscript{217,339}

Oral bisphosphonates do not cause acute renal insufficiency or acute renal failure but should not be used in patients with stage IV or V chronic kidney disease unless adynamic bone disease or other forms of chronic kidney disease and bone mineral disorder have been ruled out.

Unlike the bisphosphonates, denosumab is not excreted through the kidneys.\textsuperscript{340} The incidence of adverse events related to renal toxicity observed in the trials for preventing SREs in patients with bone metastases was lower in the denosumab arms than in the zoledronic acid arm, and was similar to that seen in the observational arms of prior bisphosphonate trials.\textsuperscript{115} The long-term effect of denosumab on kidney function is unknown. Denosumab has not been tested in patients with severe renal dysfunction.

**Acute-Phase Response**

Acute-phase reactions are typified by fever and flu-like symptoms. These symptoms are treated with over-the-counter medications, such as acetaminophen or a nonsteroidal anti-inflammatory drug; typically resolve spontaneously within 24 to 48 hours; and do not recur after first or second infusions.\textsuperscript{341} These symptoms are seen almost 3 times more frequently with intravenous bisphosphonates than with denosumab. In clinical trials, the incidence of acute-phase reactions is reported to be 27.3% with zoledronic acid versus 10.4% with denosumab in patients with breast cancer,\textsuperscript{115} and 18% with zoledronic acid versus 8% with denosumab in patients with prostate cancer.\textsuperscript{289}

**Hypocalcemia**

Hypocalcemia, the presence of low serum calcium levels, is a known adverse effect of drugs that reduce bone remodeling (antiresorptives), including bisphosphonates and denosumab. The incidence of
hypocalcemia is higher with denosumab than with zoledronic acid. In a trial of patients with metastatic prostate cancer, the incidence of hypocalcemia with denosumab was 13% versus 6% with zoledronic acid (P<.0001). A postmarketing report has detailed severe persistent hypocalcemia in patients with advanced prostate cancer and a large burden of skeletal disease. Among patients with metastatic breast cancer, the reported incidence of hypocalcemia with denosumab was 5.5% versus 3.4% with zoledronic acid. The risk of hypocalcemia seems increased in those with abnormal renal function. Symptoms of hypocalcemia include paresthesias or muscle stiffness, twitching, spasms, or cramps. Patients with conditions that affect mineral metabolism, such as those with diminished renal function, may be particularly at increased risk. Although hypocalcemia is generally seen within the first 6 months of treatment, it may occur at any time during denosumab therapy. Late onset of hypocalcemia has also been reported. In September 2012, the FDA issued a warning letter highlighting the risk of severe symptomatic hypocalcemia with denosumab treatment. Osteoclast-targeting agents should be administered with concurrent calcium supplementation and monitoring of serum calcium levels.

**Osteonecrosis of the Jaw**

ONJ is a rare but debilitating adverse effect associated with long-term use of antiresorptive agents. ONJ has been reported in patients with advanced cancers involving the bone undergoing treatment with denosumab, with an incidence not statistically different from, although numerically higher than, that seen with intravenous bisphosphonate therapy (1.8% vs 1.3%). A much lower incidence of ONJ (0%–0.4%) has been reported with the less-frequent dosing schedule of intravenous bisphosphonate therapy used for preventing cancer therapy–related bone loss (every-6-month dosing) compared with the monthly dosing used for bone metastases. More than 90% of cases of bisphosphonate-related ONJ to date have occurred with intravenous bisphosphonate therapy; the prevalence among patients receiving this therapy has been estimated to range from 1% to 5%.

The risk of developing ONJ increases with the duration of therapy. Risk factors for ONJ include recent dental extractions, oral surgery, poor dental hygiene, poorly fitting dentures or dental appliances such as bridges, oral trauma, and radiation to the jaw bone. Symptoms of ONJ include tooth or jaw pain, pain with eating, a feeling of loose teeth, swelling of the jaw, ongoing or recurrent infections, and exposure of bone seen on physical examination. The most common location of ONJ is the mandible, although it can affect the maxilla. The American Association of Oral and Maxillofacial Surgeons published recommendations to reduce the risk of ONJ, including obtaining a baseline dental examination; completing invasive dental surgery before beginning bisphosphonate or denosumab; attempting to achieve optimal periodontal health; encouraging patients to maintain good oral hygiene; monitoring for exposed bone on clinical examination; and considering discontinuing bisphosphonates for 3 months prior and 3 months after invasive dental surgery to potentially help lower the ONJ risk. Antiangiogenic therapy has also been associated with an increased risk of ONJ.

The NCCN Bone Health Task Force recommends that patients be advised to get a screening dental examination and complete any major dental surgeries before initiating intravenous bisphosphonates or denosumab when used in a monthly dosing schedule for treating bone metastases. The prospective SWOG S0702 trial is currently recruiting 7000 patients with metastatic bone disease treated with zoledronic acid to investigate risk factors, incidence, outcome, and mechanisms associated with ONJ (ClinicalTrials.gov identifier: NCT00874211).

**Atypical Femoral Fractures**

Over the past few years a small but concerning number of cases of atypical fractures in the subtrochanteric or shaft (diaphysis) regions of the femur have been reported in patients on long-term bisphosphonate therapy. Two cases of atypical fractures have also occurred in an extension study of denosumab for osteoporosis. The incidence seems to be related to duration of use, with a steep rise after 5 years of use in one analysis. Atypical femoral fractures account for fewer than 1% of all hip and femoral fractures. These fractures have a transverse or short oblique orientation and are associated with hypertrophy of the cortex in the shaft; they may be bilateral. These features are fundamentally different from common osteoporotic femur fractures and strongly suggest a distinct pathogenesis. Clinicians should be aware that these fractures may present with a prodrome of new-onset anterior thigh or groin pain (which could herald a stress fracture of
the lateral femoral shaft) before the occurrence of full fracture. Other risk factors include steroid use, rheumatoid arthritis, and combined antiresorptive therapy. Given the antiresorptive effect of tamoxifen in postmenopausal women, adding a potent antiresorptive (bisphosphonates or denosumab) to tamoxifen in the postmenopausal setting should generally be reserved for women at high risk of fracture (usually older). The pathophysiology of atypical fractures from long-term antiresorptive therapy is still under investigation.

**Atrial Fibrillation**

Atrial fibrillation has emerged as a possible concern in association with bisphosphonate use. The HORIZON pivotal fracture trial reported a higher risk of serious atrial fibrillation for patients receiving zoledronic acid at 5 mg yearly compared with those receiving placebo (1.3% vs 0.4%). This finding prompted additional reviews, and data are conflicting regarding risk of atrial fibrillation with bisphosphonates. A large-scale population-based study using the SEER-Medicare database reported a slightly increased risk for atrial fibrillation, supraventricular tachycardia, and stroke in patients with cancer receiving intravenous bisphosphonates. Atrial fibrillation was not more common in other studies of patients with osteoporosis in which zoledronic acid was dosed at 5 mg yearly. Additionally, in studies in which 4 mg of zoledronic acid was administered every 3 to 4 weeks for preventing SREs in patients with skeletal malignant involvement, no increase was seen in atrial fibrillation. In response to the concerns of atrial fibrillation, the FDA concluded that no clear association was observed across all studies between overall bisphosphonate exposure and the rate of serious or nonserious atrial fibrillation, and that increasing the dose or duration of bisphosphonate therapy was also not associated with an increased rate of atrial fibrillation.

**Adverse Effects Specific to Denosumab**

The adverse effects reported in clinical trials of denosumab varied depending on the schedule of administration. At the lower dosing schedule of denosumab that is used for bone loss and osteoporosis (60 mg subcutaneously every 6 months), the adverse effects that were significantly more common in women assigned to denosumab than placebo in the pivotal phase III trial were eczema (3.0% vs 1.7%), cellulitis requiring hospitalization (0.3% vs <0.1%), and flatulence (2.2% vs 1.4%). For the treatment of bone metastases, the recommended denosumab dosing schedule is 120 mg subcutaneously every 4 weeks. No difference is apparent in the risk of infectious adverse events (43.4% vs 42.9%) or infectious serious adverse events (11.6% vs 10.9%) with denosumab compared with zoledronic acid across all comparator trials in patients with cancer and bone metastases. Frequent adverse effects associated with this dosing schedule include fatigue, asthenia, hypophosphatemia, and nausea.

**Summary and NCCN Recommendations**

The evidence of common and uncommon adverse effects associated with these drugs is continuing to accumulate. The risks versus benefits of antiresorptive therapy must be carefully weighed before initiating therapy.

Before choosing the antiresorptive therapy, it is important to remember that renal toxicity, hypocalcemia, and ONJ occur more often with intravenous bisphosphonate therapy than with oral bisphosphonate use. Bisphosphonates are contraindicated for patients with creatinine clearance less than 30 mL/min. Oral bisphosphonates should be avoided in patients with esophageal emptying disorders or who are unable to sit upright, because these patients are at high risk for pill esophagitis. These toxicities increase with cumulative doses. Denosumab does not seem to cause renal toxicity and may be given regardless of creatinine clearance less than 30 mL/min. Oral bisphosphonates should be avoided in patients with esophageal emptying disorders or who are unable to sit upright, because these patients are at high risk for pill esophagitis. These toxicities increase with cumulative doses. Denosumab does not seem to cause renal toxicity and may be given regardless of creatinine clearance (except for patients with end-stage renal disease in whom adynamic bone disease is clinically suspected). An important caveat is that patients with renal insufficiency have a higher risk for hypocalcemia when treated with potent antiresorptives such as denosumab and zoledronic acid.

Patient education regarding rationale for treatment, the benefits versus risks of treatment, associated toxicities, and common toxicity symptoms is crucial. Patients must be encouraged to make appropriate lifestyle modifications (see “Management of Bone Health in Patients With Cancer,” page S-7) and maintain a good exercise regimen. Patients with osteoporosis or osteolytic metastasis to a vertebral body must be cautioned against performing flexion exercises of the spine. Referral to a physical therapist who understands bone health in patients with cancer should be considered for appropriate exercise recommendations.
### Table 4 Safety Considerations and Recommendations for Patients Undergoing Therapy With an Antiresorptive Agent

<table>
<thead>
<tr>
<th>Antiresorptive Agent</th>
<th>Safety Considerations/Recommendations</th>
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| **Intravenous bisphosphonates** | Acute-phase reactions  
- Counsel patients on symptoms: flu-like symptoms, myalgias, arthralgias, and fever  
- Usually occur within the first 3 d, usually resolve within 3 d after onset  
Renal toxicity  
- Monitor renal function before and during therapy  
- Maintain adequate hydration; monitor creatinine levels before each infusion  
- Consider reduced doses for patients with baseline creatinine ≤60 mL/min  
- Contraindicated for patients with creatinine <30 mL/min  
Osteonecrosis of the jaw  
- Emphasize prevention  
- Before starting antiresorptive agents  
  ➤ Obtain baseline dental examination  
  ➤ Complete invasive dental surgery  
  ➤ Achieve optimal periodontal health  
- Maintain good oral hygiene  
- Monitor for jaw/tooth pain; exposed bone on clinical examination  
- Consider discontinuation of oral bisphosphonates for 3 mo before and 3 mo after elective invasive dental surgery to lower risk of osteonecrosis of the jaw  
Hypocalcemia  
- Monitor serum calcium, magnesium, and phosphate during therapy  
- Supplement with adequate calcium and vitamin D to decrease risk of bisphosphonate-induced hypocalcemia and maintain bone health  
Atypical femur fracture  
- Counsel patients to report new thigh or groin pain  
Adherence  
- Counsel on adherence  
- Consider difficulties around dosing:  
  ➤ Must be taken with 6–8 oz plain water at least 30 minutes before first food/drink/medication  
  ➤ Potential for esophagitis  
  ➤ Calcium supplements/antacids can interfere with absorption  
Hypocalcemia (as described for intravenous bisphosphonates)  
Osteonecrosis of the jaw (as described for intravenous bisphosphonates)  
Atypical femur fractures (as described for intravenous bisphosphonates)  
| **Oral bisphosphonates** |  
| **Denosumab** |  
|  
| Acute-phase reactions  
- Less frequent with denosumab  
- Counsel patients on symptoms: flu-like symptoms, myalgias, arthralgias, and fever  
Renal toxicity  
- Denosumab is not excreted through the kidney therefore, less frequent with denosumab  
- Monitoring of renal function/dose adjustments are not indicated per package insert  
- Denosumab may be an option for patients with renal failure and renal insufficiency  
- Patients with creatinine <30 mL/min or receiving dialysis are at higher risk for severe hypocalcemia (consider adequate calcium and vitamin supplementation, correct abnormalities before treatment)  
Atypical femur fractures (as described for intravenous bisphosphonates)  

Sports Medicine recommends the patients “avoid inactivity” and provide guidelines for exercise training that is safe during and after cancer treatments. An ongoing randomized trial is studying a modular multimodal exercise program in patients with prostate cancer and bone metastases (ClinicalTrials.gov identifier: NCT01410656).

Before initiating treatment with an antiresorptive agent for cancer therapy–induced bone loss, the levels of calcium and vitamin D should be checked. Checking the 25(OH) D levels and repleting stores of vitamin D before therapy with these agents is also highly recommended because hypocalcemia has been reported in patients with unrecognized vitamin D deficiency. In addition, improved response to bisphosphonate therapy has been reported when vitamin D levels are optimized. Existing hypocalcemia must be corrected before denosumab is initiated. To prevent hypocalcemia, all patients (especially those on denosumab) without contraindications (e.g., a history of calcium kidney stones) should be advised to continue vitamin D supplementation throughout antiresorptive therapy. In addition, calcium levels should be monitored before each dose in all patients throughout treatment.

All patients should undergo a routine oral examination before starting treatment with an antiresorptive agent, and those with risk factors for ONJ should be monitored appropriately. Patients should be advised to undergo a screening dental examination and complete any major dental surgeries before initiating intravenous bisphosphonates or denosumab when used in a monthly dosing schedule for treating bone metastases. Serum creatinine should be monitored before each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. The safety considerations and recommendations for patients undergoing therapy with an antiresorptive agent are summarized in Table 4.

References

Bone Health in Cancer Care


Bone Health in Cancer Care

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Bone Health in Cancer Care


NCCN Task Force Report


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1. True or False: The NCCN Bone Health in Cancer Care Task Force recommends using the WHO FRAX algorithm for the baseline assessment of all patients with cancer at increased risk for bone loss and fracture because of their cancer or cancer-therapy.
   a. True
   b. False

2. Pharmacologic intervention with antiresorptive agents should be strongly considered for which of the following patients?
   a. Patients with cancer at increased risk for bone loss because of therapy or age with T score < –2.0 OR FRAX 10-year fracture risk >20% for major fracture or >3% for hip fracture.
   b. Patients with cancer at increased risk for bone loss because of therapy or age with T score < –2.0 AND FRAX 10-year fracture risk >20% for major fracture or >3% for hip fracture.
   c. All patients with cancer regardless of T score or fracture risk.

3. Which of the following statements is FALSE?
   a. Vertebral fracture assessment may be helpful in the baseline assessment and follow-up of patients with very high risk of vertebral fracture.
   b. All individuals with vertebral fractures have T scores classified as osteoporosis.
   c. Vertebral fracture assessment can be performed along with bone mineral density assessment using dual-energy x-ray absorptiometry.

4. True or False: For young individuals younger than 50 years who are at risk for cancer treatment–associated bone loss, the NCCN Bone Health Task Force recommends 1200 mg of calcium (from all sources) and 800–1000 IU/d of vitamin D [the latter without checking serum 25(OH) D levels].
   a. True
   b. False

5. True or False: The dose and frequency of administration of denosumab used for treating osteoporosis is the same as that used for reducing SREs from metastasis of breast and prostate cancers.
   a. True
   b. False

6. Which of the following statements is FALSE?
   a. In clinical trials of premenopausal women, both raloxifene and tamoxifen have been shown to cause a decrease in bone mineral density.
   b. Calcitonin is not recommended in the setting of bone loss from cancer therapies, except optionally for short-term use after acute osteoporotic vertebral fracture because of demonstrated analgesic effects in this setting.
   c. Parathyroid hormone (1-34) or teriparatide is a treatment option for osteoporosis in patients with increased baseline risk of osteosarcoma, such as those with Paget disease of bone, open epiphyses, or prior radiation therapy involving the skeleton (which includes many patients with cancer).

7. True or False: The 12-month results from the E-ZO-FAST trial provide further evidence that upfront zoledronic acid not only prevents bone loss but also increases bone mineral density, with a mean increase of 2.7% at the lumbar spine and 1.7% at the hip.
   a. True
   b. False

8. Which of the following statements regarding imaging of bone metastases is FALSE?
   a. If bone marrow infiltration is suspected, 18F-FDG PET or MRI is the best way to follow and evaluate disease in the bone.
   b. Lesions present on MRI or PET, such as osteolytic lesions, may not be visible on 99mTc bone scans.
   c. 18F-FDG PET assesses the metabolic activity of the metastatic tissue directly rather than the bony response to the presence of the metastasis.
   d. Interpreting imaging modalities for bone metastases requires simultaneous review of all relevant imaging studies with full clinical context.

9. True or False: 223Ra is FDA-approved for treatment in men with symptomatic metastatic castration-resistant prostate cancer that has spread to the bone but not to other organs.
   a. True
   b. False

10. Which of the following statements is FALSE?
    a. Surgical management of bone metastases is performed to relieve pain, provide stabilization, and prevent impending fracture or spinal cord compression.
    b. Fractures within the femoral diaphysis cannot be stabilized using intramedullary nailing.
    c. EBRT is widely used for patients with cancer who present with localized bone pain.

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