guideline summaries

Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline Summary

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In 2019, there are approximately 16 million cancer survivors in the United States and approximately 32 million worldwide.[1] These cancer survivors in the United States are increasingly in their sixth, seventh, and eighth decade of life. The two largest groups of cancer survivors are women with early-stage breast cancers and men with nonmetastatic prostate cancers, and these patients frequently have received cancer treatments that cause particularly high rates of bone loss. It is the coalescence of cancer survivors and osteoporosis, a health problem of near-epidemic proportions, that forms the underlying rationale for this evidence-based guideline.

The prevalence of osteoporosis worldwide is estimated at 200 million people. At least 40% of postmenopausal women and 15% to 30% of men will experience a fragility fracture.[2] Osteoporosis can be thought of as an equation.[3] The equation, simply stated, is the peak bone mass achieved by age 30 years minus the ongoing losses related to age and menopause. Osteoporosis is a complex genetic disease[4,5] and no genetic markers for either low peak bone mass or high later losses are yet being measured routinely in clinical settings. However, family history, especially of hip fracture, is an important predictor of fractures, as is advancing age.[6] Lifestyle factors also affect bone loss. For example, cigarette smoking and excessive alcohol consumption, as well as noncancer-specific medications (eg, glucocorticoids) promote bone loss.[7]

In patients with nonmetastatic cancer, both the disease itself, through an association with increased local and systemic inflammation, and its treatment can pose challenges to skeletal integrity. Chronic inflammation can promote increased bone loss through altered systemic bone remodeling, increased bone resorption, and impaired bone formation.[8] This is due to the effect of inflammatory mediators on the differentiation and activity of osteoclasts and osteoblasts.[7] Osteoclastogenesis and osteoclasts' activity can be influenced by proinflammatory cytokines, such as tumor necrosis factor, interleukin-1, interleukin-6, macrophage colony-stimulating factor, and RANK ligand.[8]

A number of cancer treatments also cause bone loss.[7] Estrogens and androgens maintain bone mass and mitigate bone loss,[9] whereas cancer treatments such as gonadotrophin-releasing hormone agonists and chemotherapy-induced ovarian failure in premenopausal women, aromatase inhibitors in postmenopausal women, and antiandrogens in men with nonmetastatic prostate cancers cause cancer-treatment–induced bone loss.[10] The estimated magnitude of bone loss due to cancer treatments is described in the guideline.[7] Bone loss that occurs with cancer therapy is more rapid and severe than postmenopausal bone loss in women or normal age-related osteoporosis in men.[10] Rates of bone loss occurring with cancer therapy can be more than seven-fold higher than in normal aging.

The purposes of the systematic review and evidence-based guideline are to evaluate randomized controlled trials and other fundamental studies reported in the literature regarding osteoporosis in cancer survivors, compare outcomes among trials, and provide guidance to clinicians on the management of osteoporosis in survivors of adult-onset cancers.[7] Additional information is available at www.asco.org/survivorship-guidelines. Patient information is available at www.cancer.net.

WHAT IS PRACTICE CHANGING

The new ASCO guideline addresses real challenges faced in clinical practice. For the cancer survivor, the guideline outlines which patients with cancer are at risk and which should undergo screening and surveillance and at what frequency. The guideline also provides clarification on when to commence treatment and offers an algorithmic approach to management, as outlined in Figure 1.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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THE BOTTOM LINE

Management of Osteoporosis in Survivors of Adult Cancers with Nonmetastatic Disease: ASCO Clinical Practice Guideline

Guideline Questions

1. Which patients with nonmetastatic cancer are at increased risk for developing osteoporotic fractures?
2. How should patients with nonmetastatic cancer who are at an elevated risk for osteoporotic fractures be screened?
3. Which patients with nonmetastatic cancer should be treated and which interventions are effective in reducing the risk of osteoporotic fractures?

Target Population

Adults with nonmetastatic cancer, including patients in active treatment (eg, receiving aromatase inhibitors [AIs], antiandrogens [ADTs], gonadotropin-releasing hormone [GnRH] agonists, or chemotherapy-induced ovarian failure [CIOF]), and long-term cancer survivors.

Target Audience

Oncologists, endocrinologists, specialists in rehabilitation, orthopedists, primary care physicians, and any other relevant member of a comprehensive, multidisciplinary cancer care team, as well as patients and their caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

CLINICAL QUESTION 1

Which patients with nonmetastatic cancer are at increased risk for developing osteoporotic fractures?

RISK

Recommendation 1.1. It is recommended that patients with nonmetastatic cancer who meet any of the following criteria should be considered at increased risk for developing osteoporotic fractures:

- Advanced age
- Current cigarette smoking
- Excessive alcohol consumption
- History of nontraumatic fractures in adulthood
- Hypogonadism
- Impaired mobility
- Increased risk for falls
- Long-term exposure to glucocorticoids
- Low body weight
- Parental history of hip fracture
- Postmenopausal status

(Type: Evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Qualifying statement. Cutoffs used to define advanced age, excessive alcohol consumption, long-term glucocorticoid exposure, and low body weight vary across studies and populations. The specifics of these continuous predictors and the thresholds most often associated with increased risk are described further in the supporting text.

Recommendation 1.2. Clinicians should be aware that the patient's anticancer therapy (eg, AIs, ADTs, GnRH agonists, or CIOF) may result in short- or long-term increased risk of osteoporotic fracture and should take anticancer therapy into account as potentially adding to baseline risk (Type: Evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 1.3. Clinicians may use a risk assessment tool (eg, FRAX; www.sheffield.ac.uk/FRAXa) to quantify the risk estimates for osteoporotic fracture in adult patients with nonmetastatic cancer. To date, existing risk assessment tools have not been validated in patients with cancer and clinical judgement is necessary in interpreting results from these tools (Type: Evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Qualifying statement. Note that several medical conditions known to cause bone loss are included in risk assessment tools such as FRAX. Clinicians who are attempting to quantify risk of osteoporosis or osteoporotic fracture should also consider additional evaluation or referral if there is a history or clinical suspicion of rarer high-risk conditions such as endocrine or metabolic causes of secondary osteoporosis (eg, hypercortisolism, hyperparathyroidism, acromegaly), disorders of collagen metabolism, and high-risk medications (or multiple moderate-risk medications) as described in the text.

CLINICAL QUESTION 2

How should patients with nonmetastatic cancer who are at elevated risk for osteoporotic fractures be screened?

SCREENING

Recommendation 2.1. Patients with nonmetastatic cancer with one or more risk factors for osteoporotic fracture, as per Recommendation 1, should be offered bone mineral density (BMD) testing with central/axial dual-energy x-ray absorptiometry (DXA). In settings where DXA is not available or technically feasible, other BMD testing (eg, quantitative ultrasound or calcaneal DXA) should be offered (Type: Evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 2.2. Patients with nonmetastatic cancer who are prescribed a drug that causes bone loss or whose baseline or subsequent BMD is near the threshold of treatment, determined using FRAX, should be offered BMD testing every 2 years or more frequently, if deemed medically necessary, based on the results of BMD testing and expected bone loss. Testing should generally not be conducted more than annually (Type: Expert Panel consensus; relative balance of benefits and harms; Evidence quality: insufficient).

CLINICAL QUESTION 3

Which patients with nonmetastatic cancer should be treated and which interventions are effective in reducing the risk of osteoporotic fractures?

TREATMENT

Nonpharmacological Intervention

Recommendation 3.1. Clinicians should encourage patients to consume a diet with adequate calcium and vitamin D. If intake of calcium (1,000 to 1,200 mg/day) and vitamin D (at least 800 to 1,000 IU/day) is not being consumed, then supplements to reach those levels are recommended (Type: Evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.2. Clinicians should actively encourage patients to engage in a combination of exercise types including balance training, flexibility or stretching exercises, endurance exercise, and resistance and/or progressive strengthening exercises to reduce risk of fractures caused by falls. Whenever possible, exercise should be tailored according to the needs and abilities of the individual patient. Patients with an impairment hindering their gait or balance should be offered medical rehabilitation (Type: Evidence-based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 3.3. Clinicians should actively encourage patients to stop smoking and to limit alcohol consumption, because smoking and alcohol consumption are risk factors for osteoporosis (Type: Evidence-based; benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Pharmacological Intervention

Recommendation 3.4. For patients with nonmetastatic cancer with osteoporosis (T scores −2.5 or less in the femoral neck, total hip, or lumbar spine) or at increased risk of osteoporotic fractures based on clinical assessment or risk assessment tools (10-year probability of 20% or greater for major osteoporotic fractures or 3% or greater for hip fractures based on the US-adapted FRAX tool), bone-modifying agents such as oral bisphosphonates, intravenous bisphosphonates, or subcutaneous denosumab at the osteoporosis-indicated dosage may be offered to reduce the risk of fracture. Hormonal therapies for osteoporosis management (eg, estrogens) are generally avoided in patients with hormonally responsive cancers. For patients without hormonally responsive cancers, estrogens may be offered along with other bone-modifying agents when clinically appropriate (Type: Evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. The current evidence suggests oral bisphosphonates, intravenous bisphosphonates, and subcutaneous denosumab are each efficacious options. The choice of which bone-modifying agent to offer should be based on several important considerations, including patient preference, potential adverse effects, quality-of-life considerations, adherence, safety for that population, cost, and availability.

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Recommendation 3.5. Provided T score and/or risk assessment (eg, FRAX-estimated fracture risk) exceed threshold values for fractures (as described in 3.4), the following specific populations may be considered appropriate candidates for bone-modifying agents:

- Premenopausal women receiving GnRH therapies causing ovarian suppression or with CIOF or who have had an oophorectomy
- Postmenopausal women who are receiving AIs
- Men who have received or are receiving ADT
- Patients undergoing or with a history of bone marrow transplant
- Patients with chronic (more than 3 to 6 months) glucocorticoid use

(Type: Evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement. The short-term bone loss associated with these conditions can be very rapid. Because of this, clinicians could consider treatment at higher bone density or T score than recommended using FRAX or similar tools, with decision-making additionally guided by anticipated losses as reviewed in the text (ie, the aforementioned bulleted conditions should be included as having "secondary osteoporosis" in the FRAX assessment tool).

Additional Resources

More information, including a supplement, slide sets, and clinical tools and resources, is available at www.asco.org/survivorship-guidelines. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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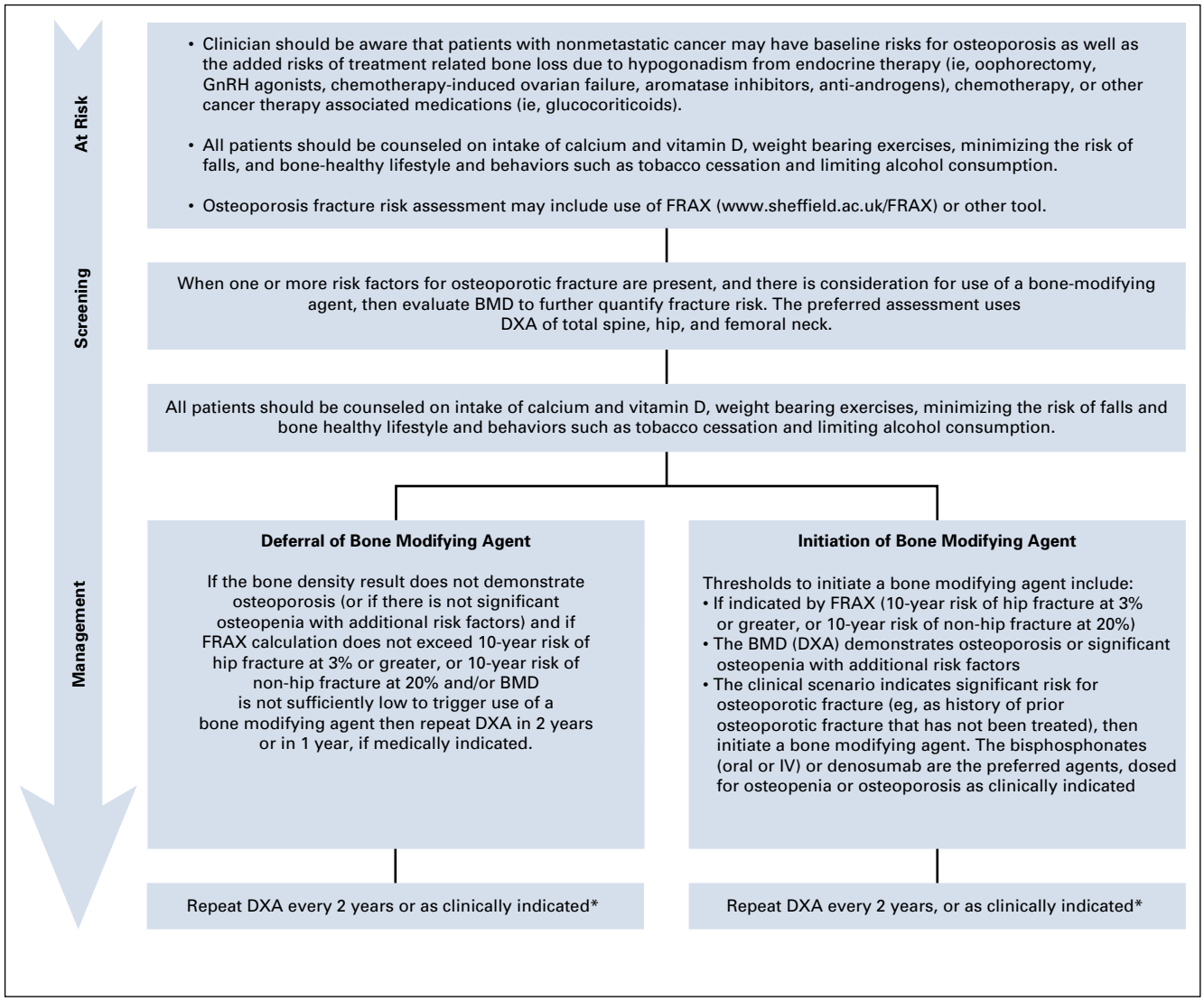

FIG 1. Algorithm for maintaining bone health in individuals with nonmetastatic cancers[11] BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry absorptiometry; FRAX, WHO Fracture Risk Assessment Tool, GnRH, gonadotropin-releasing hormone; IV, intravenous. (*) BMD should not be conducted more than annually.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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