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# Early identification and intervention matters: A comprehensive review of current evidence and recommendations for the monitoring of bone health in patients with cancer

Thomas Brodowicz [a], Peyman Hadji [b,c], Daniela Niepel [d], Ingo Diel [e,*]

[a] Department of Medicine I and Comprehensive Cancer Center, Clinical Division of Oncology, Medical University of Vienna, General Hospital, Währinger Gürtel 18–20, 1090 Vienna, Austria
[b] Department of Bone Oncology, Endocrinology and Reproductive Medicine, Northwest Hospital, Steinbacher Hohl 2–26, 60488 Frankfurt, Germany
[c] Philipps-University of Marburg, Biegenstraße 10, 35037 Marburg, Germany
[d] Amgen (GmbH) Europe, Dammstrasse 23, 6300 Zug, Switzerland
[e] Center for Comprehensive Gynecology, Augustaanlage 7–11, 68165 Mannheim, Germany

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ABSTRACT

Bone metastases are common in patients with advanced solid tumors, and many individuals experience debilitating skeletal-related events (SREs; e.g. pathologic fracture, hypercalcemia, radiotherapy or surgery to bone, and spinal cord compression). These events substantially affect disease outcomes, including survival and quality of life, and healthcare systems. Plain radiography is the most widely used imaging modality for the detection of bone metastases; skeletal scintigraphy, computed tomography, positron emission tomography and magnetic resonance imaging offer greater sensitivity but their use in routine practice is restricted by high costs and limited availability. Biomarkers of bone turnover may also have a role in the early detection of bone metastases and can provide valuable prognostic information on disease progression. SREs can be delayed or prevented using agents such as the receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor, denosumab, and bisphosphonates. Painful bone metastases can be treated with radiofrequency ablation, radiotherapy, or radionuclides such as radium-223 dichloride, which has been shown to delay the onset of SREs in men with castration-resistant prostate cancer. Close monitoring of bone health in patients with advanced cancer may lead to early identification of individuals with bone metastases who could benefit from early intervention to prevent SREs. This review examines current guideline recommendations for assessing and monitoring bone health in patients with advanced cancer, use of biomarkers and treatment of patients with bone metastases. The emerging evidence for the potential survival benefit conferred by early intervention with denosumab and bisphosphonates is also discussed, together with best practice recommendations.

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## Introduction

Bone metastases are common in patients with advanced solid tumors [1]. Cancers particularly associated with bone metastases include those of the prostate and breast (65–75% of patients) [1], and those affecting the lung (30–40%) [1] and kidney (20–32%) [1,2]. A substantial proportion of patients with advanced cancer and bone metastases will develop skeletal complications known collectively as skeletal-related events (SREs); these include pathologic fracture, spinal cord compression and hypercalcemia, as well as radiation or surgery to bone, which are surrogate markers for skeletal pain and fractures [3]. On average, patients with untreated bone metastases experience an SRE every 3–6 months [3], placing a considerable burden on both patients and healthcare systems [4]. A pooled analysis of data from phase 3 trials found that moderate/severe pain and strong opioid analgesic use generally increased in the 6 months preceding an SRE and remained elevated once the SRE had occurred [5]; pain interfered with daily living and reduced emotional wellbeing [5]. Furthermore, SREs have been associated with decreased survival [6,7]. Early detection of bone metastases is therefore important to enable optimal management of patients with bone complications secondary to cancer.

* Corresponding author.
*E-mail addresses:* thomas.brodowicz@meduniwien.ac.at (T. Brodowicz), Hadji.Peyman@khnw.de (P. Hadji), dniepel@amgen.com (D. Niepel), diel@cgg-mannheim.de (I. Diel).

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The risk of SREs can be reduced through the use of agents such as the receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) inhibitor denosumab (120 mg administered by subcutaneous injection every 4 weeks) [8] and bisphosphonates, such as zoledronic acid (4 mg administered by intravenous infusion every 3–4 weeks) [9]. Pamidronate, ibandronate and clodronate are also indicated for the prevention of SREs but only for patients with breast cancer (pamidronate and clodronate are also indicated for patients with multiple myeloma) [10–12]. Studies have shown that tumor-specific androgen pathway inhibitors, such as abiraterone acetate and enzalutamide, also have beneficial effects on bone in patients with prostate cancer, although this effect is likely to be due to their role in controlling the underlying disease rather than a direct effect on bone [13–15]. However, some patients in these studies received concomitant bisphosphonates. In addition, radium-223 dichloride (radium-223) has been shown to improve overall survival (OS) significantly compared with placebo in men with castration-resistant prostate cancer and bone metastases [16].

Early identification of patients with bone metastases is critical if the treatment options are to be best used to shift the balance from palliative treatment towards prevention of SREs, thus maintaining patients' quality of life. However, numerous factors hinder the detection of bone metastases in patients with advanced cancer, including a lack of established screening programs and differences across patient groups in terms of who seeks medical advice. For example, men are less likely than women to visit their doctor if they experience pain [17], which may delay the identification of symptomatic bone metastases in these patients. With the exception of breast cancer, general screening for bone metastases for all patients with solid tumors is not recommended (Table 1). For example, bone imaging is recommended in patients with non-small-cell lung cancer (NSCLC) or renal cell carcinoma only if symptoms suggest the presence of bone metastases [18,19]. In contrast, it is recommended that all patients with locally advanced breast cancer undergo bone imaging, regardless of whether symptoms of bone metastases are present [20,21]. The European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) joint guidelines for advanced breast cancer recommend bone imaging as part of a full staging workup for patients with advanced breast cancer, preferably with computed tomography (CT) or positron emission tomography (PET) coupled with CT (PET/CT) [20]. The guidelines also recommend that patients are managed by a multidisciplinary team that includes imaging experts [20].

In the case of prostate cancer, European guidelines recommend that only patients with intermediate- or high-risk disease should be assessed using advanced imaging techniques [22,23]. The risk of bone metastases in these patients may be assessed on the basis of prostate-specific antigen (PSA) level, disease stage and Gleason score (all at diagnosis) [24]. Guidance from the European Association of Urology (EAU) and ESMO defines the following categories of disease risk: intermediate risk – PSA level 10–20 ng/mL or Gleason score of 7 or stage cT2b disease; high risk – PSA level greater than 20 ng/mL or Gleason score of more than 7 or stage cT2c disease or higher [22,23].

Many imaging techniques are available for the detection of bone metastases, although cost, availability and expertise may vary across regions, meaning that patients may not have access to regular highly sensitive screening. New technologies for the detection of bone metastases are being developed, such as biomarkers of bone turnover, but these are not yet recommended in clinical practice. In this review, we discuss imaging and other techniques for the early identification of bone metastases, and recommendations for the early treatment of bone metastases immediately following diagnosis.

## Imaging modalities and assessment of bone metastases

The different imaging methods have advantages and disadvantages in clinical practice (Table 2) [25–28]. Plain radiography detects increased blood flow and reactive bone formation at the site of metastases but has low sensitivity and specificity. Bone scintigraphy is more sensitive than plain radiography for detecting skeletal pathology but has low specificity [29]. These techniques are relatively inexpensive and are available at most hospitals; however, the low sensitivity and specificity necessitate confirmation using other imaging modalities in patients with equivocal findings of bone metastases or a small number of hot spots [27]. Magnetic resonance imaging (MRI) is more sensitive than bone scintigraphy [28] and is the preferred method for early detection of spinal cord metastases. CT can readily distinguish osteolytic, sclerotic and soft tissue lesions, and is therefore useful during localization for biopsy and to detect bone metastases that extend into soft tissue [27]. Given the strengths and weaknesses of individual imaging modalities, there is increasing interest in hybrid techniques such as single-photon emission CT/CT, PET/CT and PET/MRI, which combine anatomical and functional information. It must be noted, however, that hybrid methods involving CT increase a patient's exposure to radiation [28]; the risk–benefit profile should therefore be considered for each patient.

Imaging is usually recommended by European guidelines only as part of disease staging, and only if there are signs or symptoms of bone metastases. Bone scintigraphy is the preferred method for detecting bone metastases (Table 1 and Fig. 1) [18–23] and recommendations for use of other imaging techniques vary among guidelines. PET is recommended as an alternative to bone scintigraphy in some guidelines [19,20,23] whereas other guidelines suggest that it should be used only if bone scintigraphy is inconclusive [21] or that it should not be used in routine practice [18,22]. MRI and CT are recommended for clinical staging in patients with high- or intermediate-risk prostate cancer [22,23], and PET/CT is recommended for screening for bone metastases in patients with advanced NSCLC or breast cancer [19,20]. PET/CT may also be used in place of CT and bone scintigraphy in some patients with primary breast cancer (those with large tumors, aggressive biology, and signs or symptoms of metastases) [21]. The guidelines for renal cell carcinoma recommend bone scintigraphy only in patients with suspected bone metastases, and advanced imaging techniques such as MRI or CT should be used only during staging [18]. Biochemical methods for detecting bone metastases are mentioned in the ESMO clinical practice guidelines for metastatic NSCLC, although the precise tests are not specified [19]. The only other guideline that recommends biochemical tests for metastases is the EAU guideline on prostate cancer, which lists bone-specific alkaline phosphatase (B-ALP) and PSA as indicators for bone metastases [22].

In line with the recommendations in European guidelines, randomized phase 3 trials in patients with breast or prostate cancer generally used bone scintigraphy and CT/MRI to identify bone metastases and SREs (spinal cord compression and pathologic fracture), although other methods, such as radiographic bone survey or clinical assessment of symptomatic SREs, have occasionally been used. Bone turnover markers were assessed in only five of the identified phase 3 clinical trials (Table 3) [13–15,30–39].

With regard to follow-up, the guidelines differ in their recommendations on how often tumors should be re-staged and whether this should include skeletal assessment. There is a lack of guidance on regular assessment for bone metastases. The EAU recommends that, for patients with prostate cancer who have received treatment with curative intent, PSA levels should be assessed 3, 6 and 12 months after treatment, then every 6 months for 3 years, and

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