Assessing response to treatment of bone metastases from breast cancer: what should be the standard of care?

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Bone is the most common site for breast cancer metastases, occurring in up to 70% of those with metastatic disease. In order to effectively manage these patients, it is essential to have consistent, reproducible and validated methods of assessing response to therapy. We present current clinical practice of imaging response assessment of bone metastases. We also review the biology of bone metastases and measures of response assessment including clinical assessment, tumour markers and imaging techniques; bone scans (BSs), computed tomography (CT), positron emission tomography, magnetic resonance imaging (MRI) and whole-body diffusion-weighted MRI (WB DW-MRI). The current standard of care of BSs and CT has significant limitations and are not routinely recommended for the purpose of response assessment in the bones. WB DW-MRI has the potential to address this unmet need and should be evaluated in clinical trials.

Key words: breast cancer, bone metastases, therapy monitoring, whole-body MRI, diffusion MRI

search strategy and selection criteria

We searched for articles focusing in PubMed on metastatic breast cancer, bone disease and response assessments between 2000 and 2014. All papers identified were in the English language, original scientific papers and review articles. We also searched the references listed for additional relevant papers.

introduction

Bone is the most common site of breast cancer metastases, with over 50% of those who relapse having it as their first site of metastases [1], and 70% of those who die of breast cancer will have evidence of bone metastases [2]. A number of biological factors account for the high frequency of bone metastases including higher blood flow in areas of red bone marrow and the production of adhesive molecules that allow binding to marrow stroma by disseminated tumour cells (DTCs). Tumour cells within haematopoietic cell niches undergo variable periods of dormancy thus evading chemotherapy, before becoming cancer-initiating cells (CICs) which become overt metastatic colonies [3]. The bone marrow also provides an ideal milieu with low partial pressures of oxygen and pH as well as high levels of extracellular calcium which promote residence and dormancy of DTCs [4, 5].

Once metastatic colonization from CICs is initiated, the normal balanced homeostatic mechanisms of bone formation and resorption, the RANK-RANKL homeostatic loop between osteoblasts and osteoclasts, becomes disrupted [6]. The binding of these two tumour necrosis factor proteins drives bone resorption by osteoclasts; this binding is regulated by the expression of the decoy receptor osteoprotegerin (OPG) [7]. The expressed imaging phenotype (osteolytic versus osteoblastic versus mixed) will depend on the dominant molecular mechanisms co-opted by cancer cells within the bone marrow [8]. The Wnt pathway/ET axis/BMP pathway has emerged as a key molecular mechanism for the development of osteosclerotic metastases and the overexpression of Wnt inhibitors [in particular dickkopfs (DKK-1) and sclerostin] and other osteoclast activators promotes the formation of osteolytic bone lesions (Figure 1). Most breast cancer metastases are osteolytic at the outset although up to 20% will have predominately osteoblastic lesions. Mixed lesions can occur frequently de novo, but are often seen as a result of ‘healing’ responses from previous therapeutic interventions.

Bone disease can have an important impact on patients’ quality of life, causing pain, pathological fractures, hypercalcaemia, anaemia and spinal cord and nerve compressions [4]. These risks are greatest among those patients with skeletal metastases but without visceral disease, perhaps partly due to a better overall survival [9]. The median survival for those with bone metastases alone has been shown to be 65 months in hormone receptor positive groups and 40 months in both the
HER-2 positive and ‘triple-negative’ groups [10]. This means that control of bony metastatic disease is vital to maintaining patient health for as long as possible. Treatments for bony metastases are generally systemic but will include local radiotherapy and surgery; all are given with palliative intent. The treatment of advanced breast cancer with bony metastases has significant health economic implications including the costs of systemic therapy (endocrine therapy, chemotherapy, bisphosphonates, monoclonal antibodies and other supportive medications), imaging, hospital admission costs for fractures and hypercalcaemia or cord compression and costs of palliative radiotherapy [11].

In order to effectively manage patients with metastatic bony disease, it is essential to have consistent, reproducible and validated methods of assessing response to therapy. These methods include clinical assessments, the use of tumour markers and imaging assessments. Radiological approaches have specific advantages including their non-invasive nature, ready access to local imaging in most cases and reproducibility.

current practice

A 10-question electronic survey (supplementary Appendix S1, available at Annals of Oncology online) of consultant oncologists who attended the UK Breast Cancer Meeting (UKBCM) 2013 was conducted with 63 respondents. Current standard of care for routine assessment of patients with established bone disease were mainly symptom evaluation (96.8%), imaging (92.1%), blood tests including bone profile (71.4%) and tumour markers (55.6%); and these were normally conducted every 3 months (74.6%). Imaging mostly used bone scans (BSs, 72.1%) and computed tomography (CT) (70.5%), although the use of localized MRI scans to areas of metastases (41%) and plain X-rays (34.4%) were also commonly utilized. Whole-body MRI was utilized by 19.7% of respondents. Imaging was mainly conducted on a 6-monthly (39.6%) or 3-monthly (35.9%) basis during active treatment, although many clinicians conducted additional imaging on symptomatic progression (37.7%). Most respondents felt that the evaluation of response and progressive disease remained difficult with a mean score of 6.7/10.
**clinical assessment**

Clinical evaluation includes assessments of pain, energy levels and mobility. Questionnaire tools to formalize clinical assessments [patient-reported outcome measures (PROMs)] which for the most part are in the form of structured measures of quality of life including items such as pain and fatigue scores have been proposed [12]. PROMs are often mandated as part of patient assessments in clinical trials but rarely used in routine clinical practice.

**tumour markers for disease assessment**

Serum tumour biomarkers proposed in the evaluation of metastatic breast cancer include the MUC-1 antigen (CA 15-3), the onco-foetal protein carcinoembryonic antigen (CEA), the oncoprotein HER-2/neu and the cytokeratin tissue polypeptide-specific antigen (TPS) [13]. Although these biomarkers are used in the detection of recurrent disease, there are limited data demonstrating their clinical utility in assessing the response of breast cancer to therapy. Indeed, only 75% of patients with metastatic disease have a raised CA15-3 [14]. One retrospective study showed that changes in CA 15-3 and CEA correlated well with response to therapy in those that were marker positive before starting treatment [15]. The best evidence comes from a large study of 526 patients looking at the use of CA 15-3 in providing additional prognostic information for response to first-line therapy in metastatic breast cancer [16]. The study showed a significant improvement in median time to progression for those that had reductions in CA 15-3 values, although many patients did not follow this trend; the authors noted that CA15-3 could not be used as the sole marker for monitoring treatment response (Figure 2). Neither of these two studies specifically evaluated patients with predominantly bone metastases. Serum biomarkers also suffer from a failure to evaluate the heterogeneity of response that is often the case in patients with multiple sites of metastatic disease. International guidelines support for CA 15-3 is variable although it may be of most use in those who have disease that is difficult to assess by other methods such as imaging [17]. Guidelines from the International Consensus Conference for Advanced Breast Cancer state that changes in tumour markers alone should not be used alone to initiate changes in treatment [18].

There are serum indicators of specific bone turnover activity that have been shown to correlate with oncologic outcome and therapeutic response. These markers report on osteoclastic/osteoblastic activity and not on tumour activity. These include the biomarkers N-telopeptide of type I collagen (NTX) and bone-specific alkaline phosphatase; elevation of these biomarkers have been shown to be associated with increased risk of skeletal-related events [19]. Reduction in NTX levels with bisphosphonate therapy have been shown to be associated with reductions in the rates of skeletal-related events and improved survival in a number of tumour types including breast cancer [20].

Of increasing recent interest for assessing response to therapy is the use of circulating tumour cells (CTC). It has been demonstrated that levels of CTCs at baseline and after chemotherapy can predict for progression-free survival and overall survival in the setting of metastatic breast cancer [21]. The use of CTCs for response assessment in metastatic breast cancer has been compared with morphologic imaging (body CT or MRI) and whole-body BSs. CTC evaluations demonstrated an advantage in predicting response to therapy.
over radiological studies in the prediction of overall survival but, of interest, there was no correlation between radiographic tumour load and CTC levels [22]. A recent study where patients switched chemotherapy if they had persistently high/increasing levels of CTCs after first-line treatment of metastatic breast cancer, did not find an increase in overall survival [23]. Of further interest is the use of CTC-free DNA which has shown early promise and evidence of superiority to CTCs in small studies of treatment response assessment in metastatic breast cancer [24].

**imaging techniques for bone disease assessments**

**bone scans**

The mainstay of bony metastatic disease evaluations remains bone scintigraphy with technetium-99m methylene diphosphonate (99mTc-MDP) [25]. Planar BSs are useful for the identification of metastatic bony disease as they are reasonably sensitive [26]. Modern extensions to BSs with SPECT or CT-SPECT improve BS performance [27, 28]. Furthermore, more modern imaging methods such as PET and whole-body MRI scans are superior to BSs in terms of lesion detection (see below). It is important to remember that 99mTc-MDP is bound to bone as part of osteoblastic activity [29] and so do not necessarily reflect on the full burden of disease within bone marrow (Figure3). The evaluation of response to therapy using BSs is thus also necessarily indirect.

Lesion detection with isotope BSs can show temporary increases in the size of detected lesions in patients who are later shown to be responding to therapy. ‘Flare’ reactions also include appearance of new lesions and thus have similar appearances on BSs to disease progression and can lead to an inappropriate changes in management [30]. Coleman et al. reported that after 3 months of systemic treatment of breast cancer, nuclear medicine consultants reported progressive disease in 12 of 16 patients that subsequently showed evidence of bone healing [31]. The biological explanation is that successful treatment leads to osteoblast healing and increased MDP BS uptake.

In order to overcome the ‘flare’ reaction, it is suggested that the BSs be repeated at a later date when the appearances of new lesions can be an indicator of disease progression (any increase in activity of persisting lesions should not be interpreted as progression without new disease) (Figure 4). The ability of BSs to positively identify response (as opposed to stable/progressive disease) is severely limited because reductions of bone activity take a prolonged period of time, limiting the timeliness of readouts. Another limitation is that the assessment of benefit in patients with very advanced disease (superscans) is impossible to do objectively because new disease cannot be confidently identified on the background of already elevated BS uptake. These limitations cannot be overcome by more recent advances in BS technology which include the BS index (tumour burden as a percentage of the total skeletal mass of a reference man), quantitative intensity normalization and segmentation of bone uptake compared with healthy controls measuring lesion area, numbers and radiotracer uptake per lesion [32].

The clinical consequences of the poor performance of BSs in assessing response include keeping patients on treatments from which they may gain no benefit for prolonged periods of time and the failure to progress patients on to other therapies that might be of more benefit, including clinical trials which require patients have documented progression before enrolment. As a result, the UK National Institute of Clinical and Care Excellence (NICE) has advised against the use of BS as a response assessment tool with the qualifying statement ‘there is no evidence that bone scintigraphy can be used to assess the response to treatment’ [11].

![Figure 3](image-url).

**Figure 3.** Multiparametric imaging of predominantly osteolytic bone disease. Multiparametric imaging assessment enables an improved understanding of the biological process driving an individual patient’s disease. It also enables the best technique to be chosen to assess responses to therapy. A 70-year-old female with a grade 2 invasive ductal carcinoma of the breast. ER positive and HER-2 negative. (Left two panels) Planar bone scan showing no abnormalities to suggest bone metastases. (Middle two panels) Multiplanar and 3D reconstructed CT scan with contrast medium administration showing multiple small osteolytic lesions (best seen on the axial image, with no associated sclerosis. (Right two panels) Morphological (T1-weighted) and projection b900 diffusion-weighted MRI scans showing widespread metastatic disease in the axial skeleton including proximal humeri, femora, pelvis, spine and ribs.
CT scans

CT play a significant role in the evaluation of metastatic breast cancer response in soft tissues by providing a means of detecting and measuring lesion sizes, extent of disease involvement and quantifying response to treatment, particularly of soft tissue disease. Most modern CT scanners can evaluate disease burden by volumetric data acquisitions and X-ray attenuation quantifications. CT measurements of soft tissue disease are incorporated into the RECIST criteria [33] but perform poorly when used to detect and assess response to therapy of bone metastases [34]. CT scans are superior to BSs for detecting bone disease [27] but their performance falls short compared with whole-body MRI scans and PET scans (see below).

Bone metastases are considered non-evaluable by RECIST criteria negating trial entry for many patients [33]. It has been suggested that CT can be used to assess bone metastases response to treatment in clinical trials providing that there is a clearly measurable soft tissue component but with important caveats. The Prostate Cancer Workgroup 2 (PCWG-2) criteria state that the response for bones be separately assessed to soft tissue disease, and that bone changes be assessed by the use of waterfall plots rather than be evaluated using standard response categories [35]. These PCWG-2 criteria have been validated in prostate cancer in recent clinical trials [36] but no similar criteria exist for breast cancer.

The development of bone sclerosis within metastatic lesions has been suggested as a method for assessing response within the MD Anderson Cancer Center criteria [37]. These criteria recognize that bone structure rarely normalizes with effective therapy and that an osteosclerotic reaction of a lytic lesion can be used as response criterion as it can represent a healing response. Using the MDA criteria, the development of new osteosclerotic lesion(s) should not be classified as progression unless there is other evidence of disease progression. These criteria do not incorporate objective measurements of CT density and patients receiving anti-osteoclastic therapy are ineligible for evaluation thus negating the majority of breast cancer patients with bone disease, as bisphosphonate treatments are standard of care. Spectral CT using dual-energy systems also provide a potential future role for the evaluation of metastatic marrow with initial data showing high detection rates but response assessment studies have not appeared in the literature [38].

PET scans

There are three classes of positron emission tomography (PET) radionuclide in use for bone imaging: a bone-specific tracer such as 18F-sodium fluoride which acts as a marker of osteoblastic action just like a BS [39], breast cancer-specific tracers such as HER-2 neu or 18F-fluoroestradiol and metabolic tracers such as [18F]2-fluoro-2-deoxyglucose (FDG) which measure the elevated glucose uptake and retention seen within tumours [40], 18F-fluoromethylcholine which measures membrane phospholipid synthesis and degradation and 18F-fluorothymidine which is a measure of cellular proliferation (but is also taken up by proliferating normal bone marrow cells) [41].
FDG is the most commonly used tracer and can be used to evaluate any malignancy that has accelerated glucose metabolism [40] including breast cancer. FDG–PET has also been used to assess the response of metastatic disease. It has potential advantages over anatomical imaging in displaying changes in metabolic activity that may occur before changes in CT–depicted morphology, although it performs poorly at certain sites such as the liver and brain where there is high background uptake. A retrospective study with FDG–PET evaluated 28 patients with bone dominant disease and demonstrated correlations between reductions in lesion FDG uptake and patient time to progression [42]; this was not compared with conventional imaging methods. A similar study, this time with FDG–PET/CT, looked at 102 patients with bone metastases from breast cancer the majority of whom were treated with hormonal therapy [43]. Reductions in specific uptake values were predictive for response duration. A more detailed serial imaging study of 25 patients with both bone and extra-bone metastases demonstrated that patients who had a homogeneous response on PET/CT to therapy had an increased time to progression (11 versus 6.5 months) [44]. Thirty per cent of patients had discordant responses between bony and extra-bone disease mostly because the bony disease did not respond, and these patients progressed more quickly, although not as quickly as those whom had a homogeneous non-response.

Clearly, FDG–PET can be only be helpful for assessing bone response in patients who have positive scans and so cannot assess specific response of FDG non-avid disease, which has been shown to occur in up to 42% of patients [45]. Bone marrow FDG–PET ‘flare’ reactions have also been described when granulocyte colony-stimulating factor is used to prevent or to treat therapy-associated neutropenia. Furthermore, FDG–PET ‘flare’ reactions have also been described 7–10 days after the start of tamoxifen/fulvestrant therapy in ER-positive breast cancers, and such an observation can indicate eventual success of therapy [46, 47]. NICE has advised against the use of FDG–PET stating that ‘there is no evidence that monitoring with PET–CT improves management compared to standard imaging modalities’ [11]. The most recent European guidelines addressing response to therapy in bone disease has concluded that ‘the role of PET–CT in monitoring bone response to therapy has been reported in a few small studies and appears potentially promising; however, prospective trials are needed to establish its true clinical utility’ [48].

MRI

Magnetic resonance imaging (MRI) has a role to play in the diagnosis and assessment of response of metastatic disease, and in particular bony disease. The key advantage of MRI is that the bone marrow can be directly evaluated using a variety of sequences. MRI sequences can be designed to be sensitive to different aspects of bone and bone marrow such as the cellular density of the bone marrow [diffusion-weighted (DW) MRI], vascularity [dynamic contrast-enhanced MRI], trabecular bone density (ultra-short echo time MRI and susceptibility weighted MRI) and bone marrow fat : water ratio (Dixon MRI, MR spectroscopy) can all be evaluated. Another advantage of MRI is the ability to perform multi-region including whole-body studies. Furthermore, techniques can be combined within the same examination thus enabling morphologic and multifunctional (sometimes quantitative) assessments of tumour response, which can be repeated as often as required as there is no radiation exposure penalty.

Several meta-analyses show that the performance of MRI is comparable with FDG–PET, both being significantly more accurate than BSs and CT for detection of bone metastases in all cancers on a per-patient and per-lesion basis [49–51]. Yang et al. showed that metastatic disease detection on a per-patient basis, the pooled sensitivity estimates for PET, CT, MRI and BS were 89.7%, 72.9%, 90.6% and 86.0%, respectively. The pooled specificity estimates for PET, CT, MRI and BS were 96.8%, 94.8%, 95.4% and 81.4%, respectively [49] (Figures 3 and 5).
The high performance of whole-body MRI can in large part be ascribed to the emerging technique of WB DW-MRI [51] (see below). Li et al. showed WB DW-MRI in comparison to PET/CT had similar sensitivity (89.7% versus 89.5%) and specificity (95.4% versus 97.5%) for disease detection [51].

A number of morphologic criteria for bone disease progression and response are described [8]. Progression criteria include new focal/diffuse area(s) of metastatic infiltration within normal marrow, increase in number/size of focal lesions, evolution of focal lesions to a diffuse neoplastic pattern, appearance of or increases in soft tissue associated with bone disease. The appearance of new fractures (requiring radiotherapy/surgical intervention as skeletal-related events) should only be considered as progression if the bone marrow signal intensity is malignant. Regression of the above findings with treatment can be considered as signs of response as should the emergence of intra/peri-tumoral fat within/around lesions (fat dot/fat halo signs), decreases in contrast enhancement and the development of dense lesion sclerosis (edge to edge) with sharply defined/very thin or disappearance of hyperintense rims on T2W fat-suppressed MR images.

There is however limited evidence for the use of morphologic MRI criteria for the assessment of bony response to treatment. A study evaluating 109 MR examinations on breast cancer patients with bony metastases found that it was possible to accurately predict progression in 79% of cases and stable disease in 75% of cases, but could not predict regression of disease [52]. This and other small studies have described a number of problems of using morphologic descriptors of response which include arrested resolution of abnormalities despite effective therapy (presumed to be due to bone sclerosis, marrow fibrosis or due to necrosis). Other limitations of morphologic imaging include the problem of evaluating disease activity on scarred background is problematic (i.e. progression can only be documented by the emergence of new disease on previously uninvolved marrow), differences in standardizing methods between centres and MRI manufacturers, and the so-called T1W image pseudo-progression phenomenon that occurs due to intense bone oedema secondary to massive cell kill and inflammation, which can lead to darkening of the bone marrow on T1-weighted sequences. Ollivier have described these technical bone marrow changes in some detail [53] but the clinical data for the use of morphological MRI in the routine assessment of metastatic bony disease response is still lacking.

**whole-body diffusion-weighted MRI**

DW-MRI measures water diffusivity without the use of contrast agents. Modified fat-suppressed T2-weighted sequences are adapted by using additional diffusion-sensitizing gradients with differing amplitudes (b-values) which allows the calculation of tissue water diffusivity [apparent diffusion coefficient (ADC) value (unit: µm²/s)] [54]. Two kinds of images are produced: quantitative ADC maps and qualitative DW images (with different b-values). High b-value images can be reconstructed using maximum intensity projections (MIPs) to appear ‘PET-like’ showing the distribution of malignant disease (Figure 6). Blackledge et al. have described a semi-automated segmentation tool to derive tumour volume and global ADC to allow objective response assessments of bone metastases [55].

DW-MRI is able to evaluate microscopic tissue water motion average at the mm scale of MR images. The ADC value reflects...
the degree of freedom of water movement at the cellular level, which is determined by architectural tissue properties such as cellular density, cellular arrangements, vascularity, extracellular space tissue viscosity and nuclear:cytoplasmic ratio. The high cellular density from increased tumour cell proliferation reduces ADC values [56]. Of particular interest in the current context is the ability of ADC to assess response to therapy. The process of cell death and apoptosis causes disruption of cell membranes increasing water diffusivity [57].

DW-MRI for the whole body has recently become practical due to technological advances [58–60]. Whole-body DW-MRI (WB-DWI) has emerged as a promising bone marrow assessment tool for detection and therapy monitoring of bone metastases [60–62]. WB-DWI can be carried out in reasonably short data acquisition times (15–25 min depending on scanner capabilities). On WB-DWI infiltrative/lytic skeletal metastases appear as focal or diffuse areas of high-signal intensity on high b-values images on a background of lower signal intensity of the normal bone marrow. It is important to emphasize that metastases detection on WB-DWI should always be corroborated by appearances of morphologic sequences in order to avoid pitfalls [63]. A recent meta-analysis demonstrated that the high sensitivity of WB-DWI to detect metastases was at the expense of specificity [64]. Thus, the pooled sensitivity/specificity of whole-body MRI (with DWI) has been reported as 87.7% [95% confidence interval (CI) 76.3% to 94.9%] and 86.1% (95% CI 79.2% to 91.4%) compared with 90.9% (95% CI 84.3% to 95.4%) and 96.1% (95% CI 92.2% to 98.4%) for whole-body MRI without DWI.

Both pre-clinical and small-scale clinical studies indicate that WB-DWI can be a useful tool for the assessment of therapy response in malignant bone marrow disease. A mouse model of breast cancer with bone metastases has demonstrated the utility of ADC measurements in assessing response to chemotherapy [65]. Similar findings have been achieved in a mouse model of Ewing Sarcoma which assessed response in lung and bone metastases in particular [66] and in a prostate cancer bone metastases mouse model [67].

A clinical study of 35 patients with osteosarcomas was able to demonstrate that post-chemotherapy ADC values were greater in those patients with a good response (t = 8.995, P < 0.01) [68]. A similar study of 11 patients with osteosarcomas also showed an increase in ADC with chemotherapy which was also related to the degree of tumour necrosis [69]. A further study in primary bone cancers also found an association between the change in ADC and tumour necrosis with treatment (P = 0.003) [70]. WB-MRI has also been studied in myeloma, where 95% of responders had an increase in ADC and 100% of non-responders having a decrease (P = 0.002) [71]. There was also a significant negative correlation between change in ADC and change in laboratory markers (r = −0.614, P = 0.001). Two small studies of metastatic bony disease in prostate cancer looking for response assessments have had mixed results [72, 73]. The first study found that mean ADCs of lesions increased significantly in response to hormonal therapy in keeping with a PSA response [73]. However, there was also noticeable spatial heterogeneity within individual metastases with the centre of the tumour having the greatest increase in ADC as well as a variation between metastases in individual patients. A second study, also in the setting of bony metastatic prostate cancer, also showed significant ADC increases in both responders and progressors showing that mean ADC cannot be used as a measure of response to bony disease in prostate cancer [72]. However, data on this question are lacking in the field of bone metastatic breast cancer with anecdotal case demonstrations of utility by Padhani and Blackledge [55, 62] (Figure 6).

There is a need to assess the utility of WB-MRI in assessing response to treatment of metastatic breast cancer to the bone, in comparison to established imaging techniques. The UKBCM survey (vide supra) established that research into this area was worthwhile (mean score 8.4/10), that clinicians would want to take part in a trial comparing WB-MRI with established imaging techniques (8.4/10), would want to incorporate it into their clinical practice if WB-MRI was shown to be superior to standard imaging (8.4/10) and would change systemic therapy if progression was shown on a WB-MRI as part of a randomised study (7.7/10).

Overall it seems that MRI offers the best single modality of assessing response to therapy in bone metastases from breast cancer, with a recent European Organisation for Research and Treatment of Cancer (EORTC) position paper concluding that MRI offers a ‘one size fits all’ solution for patients who do not have substantial non-bone disease for assessing therapy effectiveness [74].

**note of caution**

There remains an important caveat regarding the early detection of treatment failure as there is little objective evidence that changes of therapy in patients who are asymptomatic/minimally symptomatic has significant impacts on quality of life and overall survival in breast cancer [23]. However, as current therapies of metastatic breast cancer improve, the earlier treatment of small volume metastases may become a more effective strategy. In metastatic prostate cancer, it has now been shown that active treatment of asymptomatic or minimally symptomatic disease leads to disease-free and overall survival benefits [75, 76] and some consensus guidelines now recommend prospective screening for metastatic disease in asymptomatic prostate cancer patients with a view to earlier active management [77].

**conclusions**

Current methods of assessment of therapy responses for metastatic breast cancer to the bone remain problematic with wide variations in clinical practice. Imaging techniques including PET scans and WB-MRI have the potential to address the unmet need of a robust methodology of tumour detection and therapy evaluation. Importantly, these new modalities allow a clear categorization of bone metastases response categories which could have potential clinical benefits; they should be evaluated in formal clinical trials and compared with the standard of care to assess their impact on clinical practice.

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**references**


