Tumour response interpretation with new tumour response criteria vs the World Health Organisation criteria in patients with bone-only metastatic breast cancer

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BACKGROUND: We compared the utility of a new response classification (MDA; based on computed tomography (CT), magnetic resonance imaging (MRI), plain radiography (XR), and skeletal scintigraphy (SS)) and the World Health Organisation response classification (WHO; based on XR and SS) in stratifying breast cancer patients with bone-only metastases with respect to progression-free survival (PFS), overall survival (OS), and clinical response.

METHODS: We retrospectively reviewed 41 patients with bone-only metastatic breast cancer and assigned responses according to the MDA and WHO criteria. We analysed whether the MDA or WHO response classifications correlated with PFS and OS.

RESULTS: With the MDA criteria, there were significant differences in PFS between patients classified as responders and those classified as nonresponders (P = 0.025), but with the WHO criteria, there were not. Neither criteria distinguished responders from nonresponders in terms of OS. MDA response criteria correlated better than WHO response criteria with clinical response assessment.

CONCLUSIONS: The MDA classification is superior to the WHO classification in differentiating between responders and nonresponders among breast cancer patients with bone-only metastases. Application of the MDA classification may allow bone lesions to be considered measurable disease. Prospective study is needed to test the MDA classification among patients with bone metastasis.

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Bone is one of the most common sites to which breast cancer metastasises (Coleman and Rubens, 1987; Hortobagyi, 1991). Up to 85% of patients with bone metastasis have other visceral metastases during the course of the disease (Coleman and Rubens, 1987; Hortobagyi, 1991). Bone is one of the most convenient and inexpensive way of assessing treatment effectiveness. With XR, currently the most convenient and inexpensive way of assessing treatment response, 3–6 months and >30–50% mineral loss may be required before changes become visible (Bellamy et al, 1987; Howell et al, 1988). In addition, although XR can depict changes in bone structure, it cannot depict the tumour itself. With SS, which reflects bone elastic activity, it can also take 6 months or longer to...
**New criteria for bone tumour response assessment**

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| Response type               | Union International Against Cancer (UICC)* | World Health Organisation (WHO)* | Revised criteria for assessment of bone response (MDA) |
|----------------------------|------------------------------------------|---------------------------------|------------------------------------------------------|
| Target diagnostic imaging  | XR Disappearance of all known disease     | XR, SS Complete disappearance of all lesions on X-ray or scan for at least 4 weeks | XR, SS, CT, MRI Complete fill-in or sclerosis of lytic lesion on XR and CT |
| Complete response          | Lytic lesions should have radiologic evidence of calcification | Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least 4 weeks | Disappearance of hot spots or tumour signal on SS, CT, or MRI Normalisation of osteoblastic lesion on XR and CT |
| Partial response           | At least 50% decrease in size of measurable lesions | As a result of the slow response of bone lesions, the classification of ‘no change’ should not be applied until at least 8 weeks have passed from start of therapy | Sclerotic rim about initially lytic lesion or sclerosis of lesions previously undetected on XR or CT |
|                            | Objective improvement in evaluable or unmeasurable lesions | Regression of measurable lesion on XR, CT, or MRI | Partial fill-in or sclerosis of lytic lesion on XR or CT |
|                            | No new lesions or progressive lesions     | Regression of lesion on SS (exclude rapid regression) | Regression of lesion on SS (exclude rapid regression) |
| No change or stable disease| Unchanged, or between 25% increase and 50% decrease in size of measurable lesions⁴ | Increase in size of existing lesions or appearance of new lesions | Decrease in blastic lesion on XR or CT |
| Progressive disease        | Mixed; some lesions persist while others progress, or new lesions appear | No change in measurable lesion on XR, CT, or MRI | No change in blastic lesion on XR, CT, or MRI |
|                            | Failure; some or all lesions progress and/or new lesions appear: No lesions regress | No new lesion on XR, SS, CT, or MRI | No new lesion on XR, SS, CT, or MRI Increase in size of any existing measurable lesions on XR, CT, or MRI |
|                            |                                         | Increase in activity on SS (excluding flare phenomena) or blastic/lytic lesion on XR or CT | |

**Table 1** The UICC, WHO, and MDA criteria for detection of bone response

**Abbreviations:** SS = skeletal scintigraphy; XR = plain radiography; CT = computed tomography; MRI = magnetic resonance imaging. *Criteria are based on plain radiography; the duration of response is to be measured from the start of therapy until either new lesions appear or any one existing lesion increases by 25% or more above its smallest recorded size. ¹Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy. ²Rapid osteolytic progression may show decreased osteoblastic activity, resulting in regression of ‘hot spots’ on SS. XR or CT may be helpful in detecting progressive osteolysis and thus helping to identify progressive disease in this situation. ³If lesions that cannot be measured but are otherwise evaluable represent the bulk of disease and these lesions clearly do not respond even though measurable lesions have improved, then the response is considered no change rather than an objective regression.

Reliably detect a response because of the confounding effect of the flare phenomenon, a spurious increase in radionuclide uptake because of reparative mineralisation around healing metastases (Coleman, 1991; Hortobagyi, 1991). Although CT is not commonly used to scan the whole body, CT can depict both structural changes in the bone and anatomic changes associated with the target tumour because of its multiple window settings. Magnetic resonance imaging is optimally suited for showing spinal cord status and changes in the bone marrow but not suited to showing lytic or blastic change in bone structure. FDG PET, which reflects high glucose metabolism, can be used to assess bone tumour response in osteolytic metastatic lesions (Du et al, 2007), but it lacks the detail necessary to detect anatomic changes in response to treatment. Positron emission tomography—computed tomography is a new method of combining metabolic and anatomic information, but it is not yet commonly available for routine screening (Even-Sapir, 2005). Thus, proper assessment of the response of bone metastases to treatment requires consideration of different aspects of the lesions, use of diagnostic imaging modalities in appropriate combinations, and use of accurate, standardised response criteria. Unfortunately, the complexities of this process have led to the practise of considering bone lesions unmeasurable disease.

Computed tomography and MRI are now commonly used in clinical practise to assess bone tumour response, but the evidence of an advantage of these imaging modalities over conventional XR or SS is limited (Hamaoka et al, 2004). Until recently, no published response criteria included findings from diagnostic CT or MRI. The two established sets of criteria for assessing bone tumour response, one from the International Union Against Cancer (UICC) (Hayward et al, 1977) and the other from the World Health Organisation (WHO, 1979), are 30 years old and based on findings from XR or SS, which, as explained earlier, are limited in that 6 months or more may be needed before responses become visible. These criteria are not adequate as they do not incorporate modern methods (e.g., CT and MRI) of assessing the response of bone metastatic lesions to treatment. Another system in broad use, the Response Evaluation Criteria in Solid Tumours classification (Therasse et al, 2000), does not include bone lesions in response assessments. Therefore, in the absence of established response criteria, current response assessments for bone lesions using CT or MRI are highly dependent on the physician’s judgment.

There is an urgent need to develop appropriate criteria for assessing tumour response in the bone because patients with bone-only metastatic disease have traditionally been excluded from clinical trials owing to the lack of such criteria. Further, the existence of an objective method with which community physicians can evaluate their patients in a timely manner and determine the effectiveness of treatment in eliciting a response in bone metastases may affect the quality of the care provided to these patients.

We hypothesised that CT or MRI is more accurate in assessing the response of bone metastatic lesions to treatment than is XR or SS because CT and MRI can visualise both bone and tumour and, presumably, changes in both that are associated with treatment (Hamaoka et al, 2004). To test this hypothesis, we compared the ability of our ‘MDA classification’, which takes into account findings from CT and/or MRI (Hamaoka et al, 2004) (Table 1), and
the WHO classification, which does not, to stratify breast cancer patients with bone-only metastases with respect to progression-free survival (PFS), overall survival (OS), and clinical response.

MATERIALS AND METHODS

This study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center. We identified 46 patients with breast cancer and bone-only metastases who were observed at MD Anderson Cancer Center and given systemic treatment from October 1991 to September 2004 and who had CT, XR, SS, and/or MRI examinations available for review (a total of 180 imaging examinations). We excluded the patients who were given bisphosphonates because such treatment might affect the appearance of bone on imaging studies. Five of the 46 patients were not included in the statistical analysis because they underwent additional treatment before the first response assessment 2–6 months after the initiation of systemic therapy. All patients participated in clinical trials or standardised treatment protocols and received systemic therapy (chemotherapy in 34 patients and endocrine therapy in 7 patients). As this study focused on comparing imaging response criteria and diagnostic imaging before and after treatment, the results should not be affected by the type of treatment or chemotherapy regimen. Images were obtained at baseline (before the start of systemic therapy) and at 2–6 months after the beginning of systemic therapy and/or at 11–13 months and/or after the beginning of systemic therapy. The broad time ranges for the two response assessment points were a result of the retrospective nature of this study. The timing of follow-up bone imaging commonly changed during the course of the study according to the tumour and treatment status.

All images were reviewed and responses assigned independently by two board-certified radiologists who specialise in musculoskeletal radiology (CMC, JEM) and who were blinded to patient identities and outcomes. A response was assigned to each imaging study (XR, SS, CT, or MRI). In addition, a response was assigned to each patient on the basis of each of the three sets of imaging response criteria (UICC, WHO, and MDA) (Table 1). The UICC criteria are based only on findings from XR, the WHO criteria include XR and SS, and the MDA criteria include findings from XR, SS, CT, and MRI (Table 1). Therefore, XR images were read three times – once in terms of the UICC criteria, again in terms of the WHO criteria, and a third time in terms of the MDA criteria. Skeletal scintigraphy images were read twice, in terms of the WHO and MDA criteria. Computed tomography and MRI scans were read only once, in terms of the MDA criteria. Responses were categorised as complete response, partial response, stable disease, or progressive disease. In total, 431 separate assessments (180 image sets) were made by each radiologist. Final responses were confirmed by consensus, with discrepant diagnoses resolved through discussion by the two readers in the presence of a third investigator. Clinical evidence of response was obtained from evaluation of (1) symptom changes, (2) trends in the levels of tumour markers, and (3) all available radiographic images. If all three criteria showed stable disease or if one or more criteria showed disease progression, the findings were interpreted as indicating no response. If one or more criteria showed response and the others were stable, the findings were interpreted as indicating a response.

To verify the advantage of the MDA criteria, we analysed whether the use of a particular imaging modality or response classification would distinguish responders from nonresponders in terms of PFS or OS by using Kaplan–Meier analyses. To analyse which particular imaging modality or response classification most accurately reflected true bone tumour response, we analysed agreement between the response assigned on the basis of imaging results (response assigned on the basis of XR, SS, CT, or MRI alone and response assigned according to the UICC, WHO, and MDA criteria) and clinical response (complete or partial response vs stable or progressive disease) using McNemar’s test and the kappa coefficient test.

The retrospective nature of the data collection prevented our obtaining enough XR and MRI scans for statistical analysis of XR or MRI as single modalities. Less number of XR synchronised images for each part by part, in turn precluded us from studying the UICC criteria, which are based only on XR. Less number of of images for each part by part precluded us from studying the UICC criteria, which are based only on XR.

Table 2 Patients’ characteristics

| Characteristic | Number (%) |
|----------------|------------|
| No. of patients | 41 |
| Age, median (range) | 42 years (31–61 years) |
| Disease stage | |
| I | 7 (17) |
| II | 21 (51) |
| III | 4 (10) |
| IV | 8 (20) |
| Unknown | 1 (2) |
| T status | |
| 1 | 11 (27) |
| 2 | 24 (59) |
| 3 | 2 (5) |
| 4 | 3 (7) |
| Unknown | 1 (2) |
| N status | |
| Positive | 27 (66) |
| Negative | 13 (32) |
| Unknown | 1 (2) |
| Estrogen receptor status | |
| Positive | 27 (66) |
| Negative | 13 (32) |
| Unknown | 1 (2) |
| Progesterone receptor status | |
| Positive | 24 (59) |
| Negative | 16 (39) |
| Unknown | 1 (2) |
| HER2/neu status | |
| Positive | 5 (12) |
| Negative | 13 (32) |
| Unknown | 23 (56) |
| Bone metastatic site | |
| Spine | 36 (88) |
| Pelvis | 18 (44) |
| Ribs | 14 (34) |
| Type of treatment | |
| Chemotherapy | 34 |
| Endocrine therapy | 7 |
| Availability of images | |
| At baseline and at 2–6 months after treatment initiation | |
| XR images | 13 |
| SS images | 37 |
| CT images | 34 |
| MRI images | 13 |
| At baseline and at 11–13 months after treatment initiation | |
| XR images | 11 |
| SS images | 22 |
| CT images | 24 |
| MRI images | 12 |

Abbreviations: XR = plain radiography; SS = skeletal scintigraphy; CT = computed tomography; MRI = magnetic resonance imaging.
synchronised MRI is caused, which it is not standard to assess bone tumour response. Therefore, the role of MRI was precluded from the analysis. In addition, few image sets were available from the later assessment time (at 11–13 months after treatment). Therefore, we compared CT vs SS (to compare diagnostic imaging) and the MDA classification, which includes CT, XR, and SS, vs the WHO classification, which includes XR and SS, for the period between baseline and 2–6 months after treatment had begun.

RESULTS

Patient characteristics

Patients’ characteristics are shown in Table 2. The median age at diagnosis was 42 years (range, 31–61 years). We did not attempt to separate patients into lytic and blastic subgroups because most bone metastases had both lytic and blastic components. The clinical response rates at 2–6 months after treatment initiation and at 11–13 months after treatment initiation were 36.6 and 30.6%, respectively. Only one patient died before 12 months after treatment initiation. The median follow-up period was 37 months.

CT vs SS

Skeletal scintigraphy alone did not distinguish responders from nonresponders in terms of either PFS (median time to progression, 10.3 months for responders vs 14.3 months for nonresponders, $P = 0.50$; Figure 1B) or OS (median survival time, 61.9 months for responders vs 59.9 months for nonresponders, $P = 0.80$). Computed tomography alone also did not distinguish responders from nonresponders in terms of either PFS (median time to progression, 19.1 months for responders vs 14.3 months for nonresponders, $P = 0.18$; Figure 1A) or OS (median survival time, 61.9 months for responders vs 34.4 months for nonresponders, $P = 0.38$).

However, CT alone tended to correlate better than SS alone with true clinical response during the first 2–6 months after treatment (kappa coefficients, 0.44 and 0.05, respectively; McNemar’s $P = 0.74$ and 0.62, respectively; Table 3).

MDA classification vs WHO classification

The MDA classification, which includes SS and CT, distinguished responders from nonresponders in terms of PFS (median time to progression, 23.3 months for responders vs 5.5 months for nonresponders; $P = 0.025$; Figure 2A). There was also a trend for difference between responders and nonresponders in terms of OS, but this difference was not significant (median survival time, 61.9 months for responders vs 34.4 months for nonresponders; $P = 0.13$).

In contrast, the WHO classification did not distinguish responders from nonresponders in terms of either PFS (median time to progression, 12.4 months for responders vs 10.4 months for nonresponders; $P = 0.55$; Figure 2B) or OS (median survival time, 61.9 months for responders vs 59.9 months for nonresponders; $P = 0.97$). The MDA criteria tended to correlate better than the WHO criteria with true clinical response during the first 2–6 months after treatment (kappa coefficients, 0.53 and 0.07; McNemar’s $P = 0.09$ and 0.81, respectively; Table 3).

DISCUSSION

We previously reported a new set of response criteria, the MDA criteria, that address the shortcomings of the UICC and WHO criteria by taking into account CT and MRI findings (Hamaoka et al, 2004) (Table 1). The MDA criteria also include detailed descriptions of anatomic changes to be considered for each diagnostic imaging modality. The MDA criteria take into account the fact that the structure of bone rarely heals such that the bone has the same appearance as the original even if treatment was
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Figure 2 Progression-free survival (PFS) curves for patients who responded to treatment (complete or partial response) and those who did not (stable or progressive disease) according to the MDA criteria (A) and the World Health Organisation (WHO) criteria (B). The MDA criteria (which incorporate findings from CT scans) distinguished responders from non-responders during the first 6 months after treatment according to PFS; in other words, patients classified as responders according to the MDA criteria (which included CT findings) had a better prognosis than did those classified as non-responders. In contrast, the WHO classification (based on SS findings) did not differentiate between responders and non-responders in terms of PFS.

significantly effective (complete response). For example, according to the MDA criteria, recalcification of the rim of an osteolytic lesion on XR or CT (Figure 3A) is considered partial response, and an increase in the area of lysis (Figure 3B) is considered progressive disease.

The results of this retrospective image reading analysis indicate that the MDA classification is superior to the WHO classification in differentiating between responders and non-responders among breast cancer patients with bone-only metastases. With the MDA classification, which takes into account CT findings, there were significant differences in PFS between patients classified as responders and those classified as non-responders within 2–6 months after treatment. With the WHO classification, which does not take into account CT findings, there were no such differences. The MDA criteria tended to be more sensitive than the WHO criteria for detecting response, although the number of cases studied was too few to permit definitive conclusions on this point. Computed tomography may be more sensitive than SS for discerning responses.

UICC criteria did not distinguish between responders and non-responders in terms of survival rates.

Despite the widespread use of CT for assessing tumour response of solid non-bone tumours, the use of CT for assessing bone tumour response has yet to be established. We did find one published prospective study in which CT was used to assess the response of lytic metastatic bone lesions in 20 patients and CT response was compared with change in patients’ symptoms (Bellamy et al, 1987). In this study, improvement observed on CT was associated with improvement in symptoms in two-thirds of the patients. This study has shown that patients with a response on CT may have had longer PFS and OS than those who did not show a response.

The lower correlation between the primarily SS-based WHO criteria and response than between the MDA criteria and response could have resulted from several factors, including high false-positive rates caused by conditions other than tumour (e.g., fracture, arthritis, infection) (Galasko and Doyle, 1972; Citrin et al, 1977; Coleman et al, 1988b; Tubiana-Hulin, 1991; Rybak and Rosenthal, 2001) or ‘flare’ phenomena (Coleman, 1991; Hortobagyi, 1991). In one prospective report, in 75% of patients with breast cancer whose bone metastases showed a partial response (healing of lytic metastases on XR), there was increased tracer uptake on SS during the first 3 months after treatment because of new bone that had formed during the repair process. Such a situation could well be interpreted as progressive disease; however, after 6 months, the accumulation gradually decreased (Coleman et al, 1988a).

Another possible explanation for the poor correlation between WHO response and clinical response is that rapid progression of disease, when overwhelming destruction allows little chance for new bone to form, is sometimes depicted by SS as a reduction in isotope uptake (‘cold spots’) (Galasko and Doyle, 1972; Condon et al, 1981; Cook and Fogelman, 2000). In our opinion, determining the final response of bone metastases solely on the basis of changes in radionuclide uptake over time is not appropriate (Libshitz and Hortobagyi, 1981).

Our findings suggest that the MDA criteria, which incorporate findings from CT scans, are superior to the WHO criteria, which are based primarily on SS, for predicting PFS in patients who respond to treatment. This confirms the importance of using multiple imaging modalities to accurately determine response.

In summary, the results of this image reading study suggest that the MDA classification is superior to the WHO classification for assessing the response of bone metastases to treatment. However, these findings need to be confirmed prospectively. In addition, in future prospective studies, the effect of bisphosphonates should be studied because bisphosphonates are now commonly used in patients with bone metastasis. Further, PET–CT, which fuses images from PET and CT, may yield better detection of bone tumour response because of the addition of information on glucose metabolism to the anatomic details provided by CT. One study showed 80.5% agreement between CT osteoblastic response and PET positivity change (positive to negative) in osteolytic metastases (Du et al, 2007). Positron emission tomography also has the advantage of permitting quantification of response – bone tumour response might be quantified using the maximum standard uptake value (Stafford et al, 2002). That indicates that PET can be a sensitive modality for monitoring osteolytic bone

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tumour response. Although PET scanning has the potential to yield false-positive results with the use of granulocyte colony-stimulating factors in patients receiving myelosuppressive chemotherapy, the CT aspect of PET–CT may compensate for that potential problem with its anatomic information (Even-Sapir, 2005; Israel et al., 2006). As the cost of PET–CT gradually becomes more reasonable, there is a great possibility that PET–CT may become the standard for assessing the response of bone metastasis.

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**Figure 3** Computed tomography scans assessed with the MDA criteria. (A) Sclerotic change (right) in the rim of an originally lytic lesion (left) indicates a partial response. (B) Lytic progression (right) of an originally lytic lesion (left) indicates progressive disease.
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