

ORIGINAL ARTICLE

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## Bone scintigraphy in the monitoring of treatment effect of bisphosphonates in bone metastatic breast cancer

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### Summary

**Purpose:** The aim of this retrospective study was to assess the possibilities of whole-body bone scintigraphy (WB BSc) in the monitoring of the effect of biphosphonate treatment in patients with breast cancer and bone metastases.

**Patients and methods:** 51 breast cancer patients with bone metastases, aged from 33 to 73 years, were included. WB BSc was performed on a Siemens DIACAM gamma camera, 2-4 h after i.v. injection of 740 MBq <sup>99m</sup>Tc-MDP, before the start of the biphosphonate treatment (baseline scintigraphy) with zoledronic acid (Zometa) and at least 6 months thereafter (control scintigraphy) in order to avoid the "flare" effect.

**Results:** At the baseline WB BSc 41 (80.4%) patients presented with multiple (over 3) bone metastatic lesions, 9

(17.6%) patients with single (up to 3) lesions and 1 (1.96%) patient with a solitary bone metastasis. All bone metastases had osteoblastic appearance. At the control scintigraphy 4 (8%) patients showed complete therapeutic response (CR; no bone lesions were visualized); 21 (41%) patients partial response (PR; decrease in the number and the intensity of the lesions); 16 (31%) patients stable bone lesions (SD; no change in the number or the intensity of the bone metastases); and 10 (20%) patients showed disease progression (PD).

**Conclusion:** WB BSc is a reliable functional imaging modality for assessment of the biphosphonate therapeutic effect and an important method in the multimodal treatment planning of breast cancer patients.

**Key words:** biphosphonates, bone metastases, bone scintigraphy, breast cancer, zoledronic acid

### Introduction

Breast cancer is the most common malignancy and the second leading cause of cancer deaths among women worldwide [1] while skeleton is the predominant site of its metastatic spread.

Since the discovery of their mineral metabolism in the bone about 35 years ago with the research by

Fleisch [2,3], biphosphonates have become the first choice for standard care in the management of bone diseases associated with hyperresorption [4].

Biphosphonates are non-metabolized compounds with high bone affinity used both in the treatment of benign and malignant bone diseases and as radiopharmaceuticals in bone imaging. They inhibit tumor-induced bone destruction and the associated hypercalcemia. The radiolabelled biphosphonate use in <sup>99m</sup>Tc-MDP scintigraphy is widely regarded as the most cost-effective and available whole-body screening test for bone metastasis pattern prompting the commencement of adjunct therapy of bone metastases. At the same time, despite some case reports about false-negative bone scans for bone metastases in breast cancer patients under biphosphonates treatment and possible competitive effect [1], other studies have shown that treatment with biphosphonates does not impair the sensitivity of <sup>99m</sup>Tc-MDP bone scintigraphy in detecting bone lesions [5].

In compliance with the long biological half-life

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of bisphosphonates in the bone, treatment response should provide a better patients' quality of life and the period of bone scintigraphy monitoring of the therapeutic effect should be evaluated with regard to the treatment strategy.

The aim of the present retrospective study was to assess the possibilities of WB BSc in the monitoring the effect of bisphosphonate treatment in breast cancer patients with bone metastases.

## Patients and methods

### Patient population

The study included 51 patients with breast cancer, aged 33 - 73 years (mean 53.3). Thirty-one patients were with right and 19 with left breast cancer and 1 had bilateral breast cancer. Some patients presented with operable disease (stage II, III) and developed bone metastases after appropriate primary treatment, including surgery and chemo and/or hormonal therapy. In those patients bone metastases were detected during the follow-up period. During the bisphosphonate treatment most of the patients continued their concomitant chemo- and/or hormonotherapy. Patients received zoledronic acid (Zometa) 4 mg by short (15 min) i.v. infusion every 3-4 weeks.

### Methods

WB BSc was performed on a Siemens DIACAM gamma camera, 2-4 h after i.v. injection of 20 mCi (740 MBq) 99mTc-MDP, 15-20 cm/min speed of the table, according to the protocol of the department. In addition, most of the patients underwent frame scintiscans on selected target areas of interest concerning the bone lesions. WB BSc was performed before the start of the bisphosphonate therapy (baseline scintigraphy) and at 6 and 12 months thereafter (control scintigraphy) in order to avoid the "flare" effect.

**Table 1.** Localization of bone metastases and corresponding response rates

Localization	Number of patients	%	CR and PR Number of patients	%
Spine	42	82.3	18	35.3
Ribs	35	68.6	12	23.5
Pelvis	28	54.9	10	19.6
Extremities	23	45.0	2	3.9
Skull	15	29.4	3	5.9
Scapula	1	1.9	1	2.0

CRs and PRs exceed 25 patients mentioned in the text, since most of them had multiple bone metastases

The effect of bisphosphonate therapy was evaluated as follows: 1) CR to the bisphosphonate therapy, when no active bone metastatic lesions were visible; 2) PR, when a decrease in the number and/or the intensity of the lesions could be detected; 3) SD, when no change in the number or the intensity of bone metastases could be observed; and 4) PD, when new bone lesions were visualized.

## Results

At baseline WB BSc 41 (80.4%) patients presented with multiple (over 3) bone lesions, 9 (17.6%) patients with single (up to 3) lesions and 1 (1.96%) patient with a solitary bone metastasis. All lesions were osteoblastic. The most involved sites were the spine (82.3% of the patients), ribs (68.6%), pelvis (54.9%), with decreasing incidence in the extremities, the flat bones of the skull and the scapulae (Table 1).

Complete therapeutic response was seen 12 months after bisphosphonate therapy in 4 (8%) of all 51 treated patients. Three (75%) of them had multiple and 1 (33.3%) single lesions at baseline WB BSc. There was a remarkably decreased 99mTc-MDP uptake in the previously seen bone lesions (Figure 1).

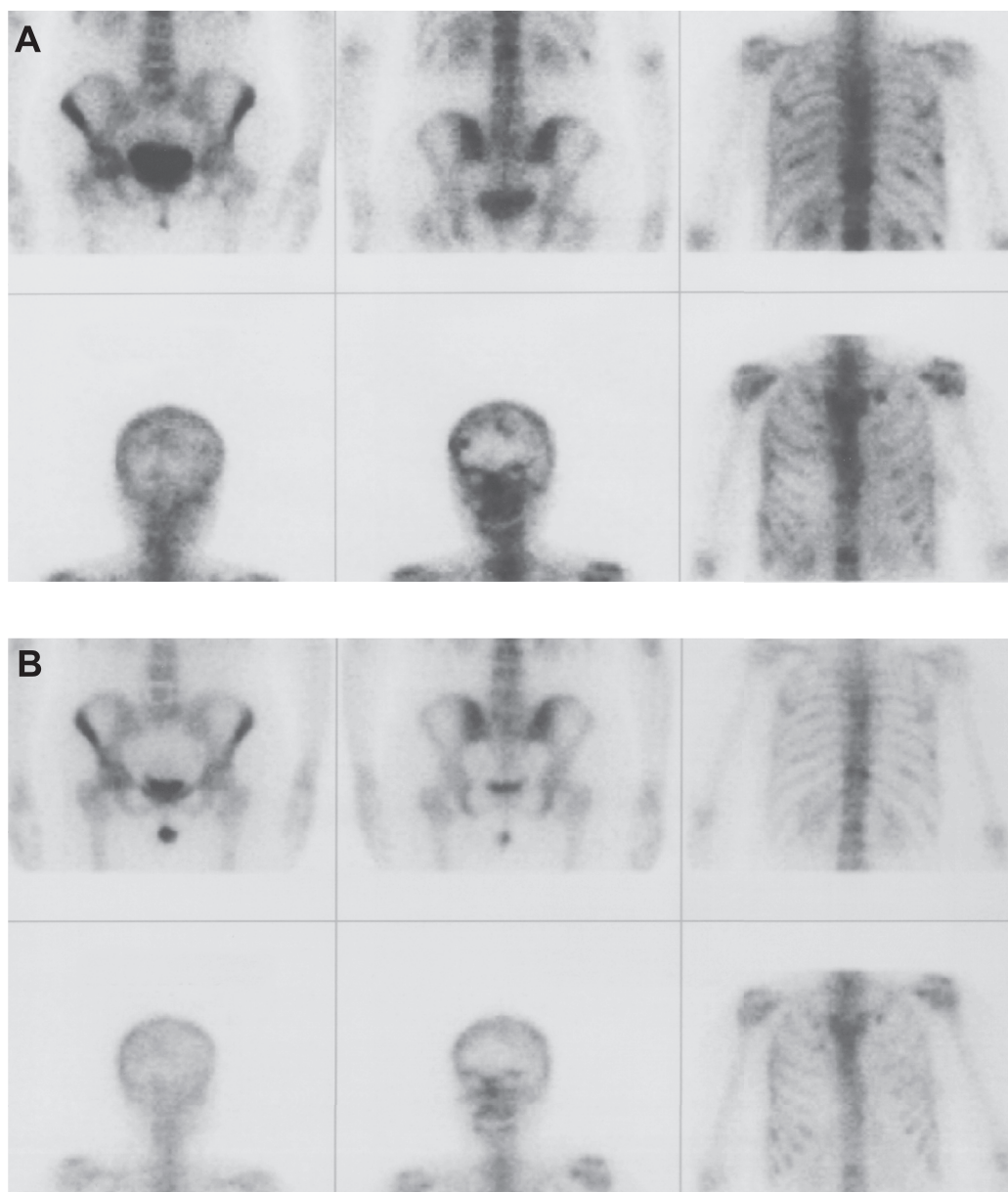
PR was established in 21 (41%) patients who showed decrease in the number and the intensity of fixation of the radiotracer in the lesions. Twenty (95.2%) of them were with multiple and 1 (4.8%) with single metastases at baseline WB BSc (Figure 2).

Sixteen (31%) patients showed SD with no change in the number or the intensity of the previously seen bone metastatic lesions. Twelve (75%) of them were with multiple and 4 (25%) with single metastases before the start of bisphosphonate treatment.

Ten (20%) patients showed disease progression on bisphosphonate treatment with appearance of new bone metastases. Six (12%) of these patients had multiple bone metastases at the baseline scan, 3 (6%) had single lesions, and 1 (2%) patient had a solitary lesion. The therapeutic response of the bone metastatic lesions to bisphosphonate therapy is shown in Table 2.

**Table 2.** Bisphosphonate treatment response of bone metastases

Treatment response	Number of patients	%
Complete response	4	8
Partial response	21	41
Stable disease	16	31
Progressive disease	10	20
Total	51	100



**Figure 1.** Complete response: female, 41-year-old, right breast cancer, neoadjuvant chemotherapy, mastectomy (1999), pT3N2M0, ER (+), PR (+), postoperative chemo-, radio- and hormonotherapy; biphosphonate therapy. **A)** Baseline scintigraphy (26.06.2002): multiple bone metastases – hyperfixating lesions in T 10, L1, ribs on the posterior surface, a lesion in the border of the right parietal and right frontal bones and a lesion with central hypofixation of  $^{99m}\text{Tc}$ -MDP and a hyperfixating rim in the left parietal bone. **B)** Control scintigraphy (26.03.2003): no active bone lesions can be seen.

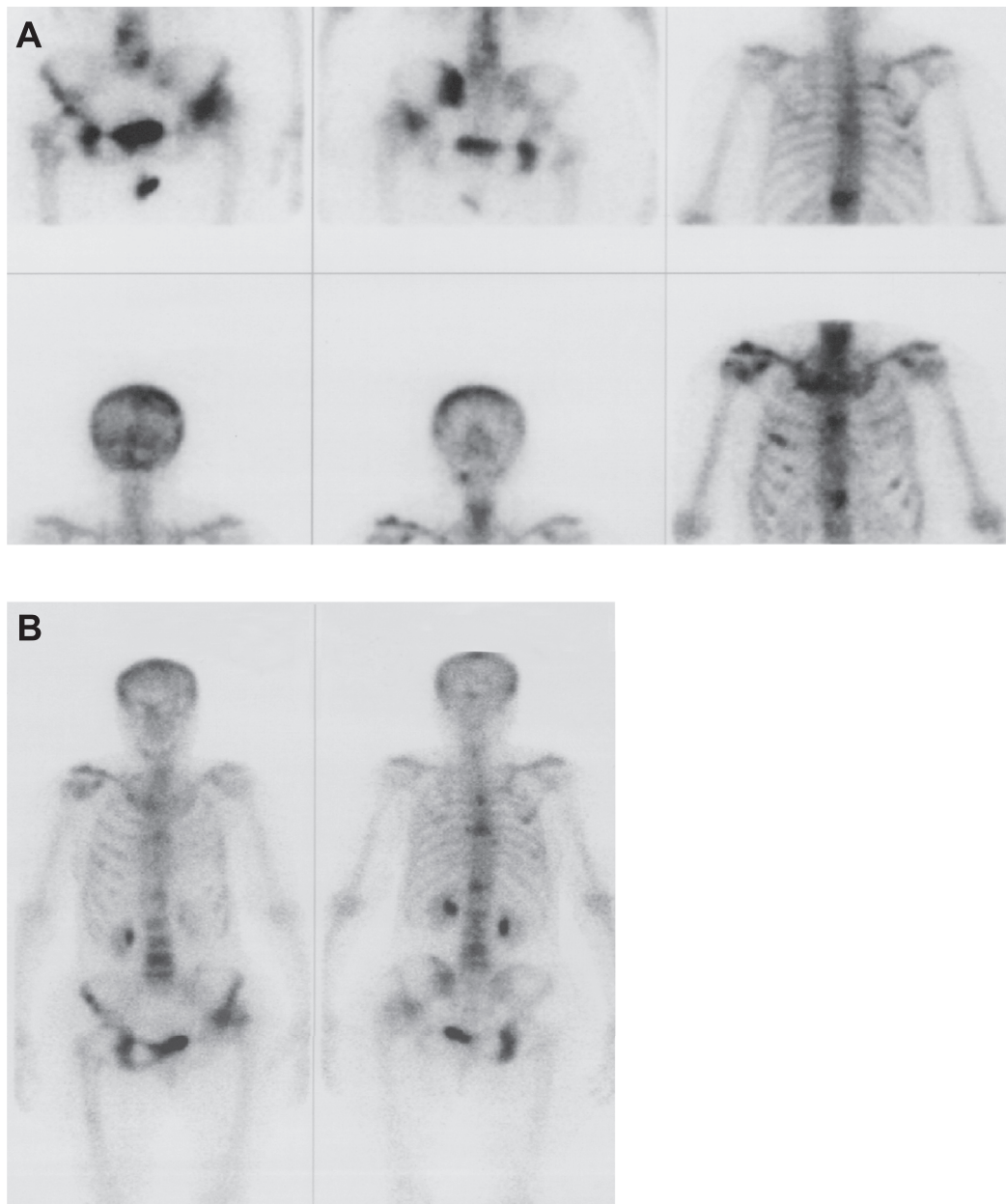
## Discussion

With the introduction of bone scintigraphy in clinical practice as an imaging modality in 1961, the visualization of the bone matrix and metabolism became possible. This functional diagnostic test appeared to precede 6 or more months from other morphologic imaging modalities such as X-ray in the initial detection of bone metastases, this being one of the main reasons why bone scintigraphy has become

the “gold standard” and the most commonly used procedure for visualization of bone metastatic lesions of malignant diseases. Early detection and rapid whole-body images at a reasonable cost are the cornerstone in bone scintigraphy advantages for bone metastases screening in breast cancer patients [6-8].

Bone tumor evaluation can be based on the clinical status, changes in the levels of biochemical markers or by using imaging studies.

Bibliographic data concerning the clinical effect



**Figure 2.** Partial response: female, 70-year-old, left breast cancer, mastectomy (1997), pT2N1M0, invasive ductal carcinoma, G2, ER 59 fmol/l, PR (-), postoperative chemo-, radio- and hormonotherapy; bisphosphonate therapy. **A)** Baseline bone scintigraphy (15.06.2004): multiple osteolytic bone metastases (hypofixation of the radiotracer) in the right parietal and occipital bones and hyperfixating osteoblastic lesions in T3,6,11, 6th right rib, L4-5, left sacroiliac synchondrosis, both acetabuli, right ischium, right shoulder. **B)** Control scintigraphy (07.02.2006): remarkably decreased  $^{99m}\text{Tc}$ -MDP uptake in the previously seen lesions and normalization of the mineral metabolism.

of bisphosphonate treatment of bone metastases in patients having breast cancer demonstrate reduction in breast cancer morbidity as a whole in a number of trials using pamidronate, zoledronate, ibandronate and clodronate [9-14]. Bisphosphonates adverse effects are generally considered mild, with relatively clear strategies to deal with [15,16]. Pain relief [17,18], including cases of chemoendocrine therapy-refractory inoper-

able metastatic breast carcinoma [19], inhibition of the extension of a bone metastasis with no detection of new lesions by WB BSc or magnetic resonance imaging (MRI) [20,21], reduction of the number of visible bone metastases after bisphosphonate treatment [22], and improved survival [23] are solid examples of monitored treatment effect. Two new studies showed definite decrease in the number of episodes with hy-



percalcemia, the rate of the skeletal-related events and/or the need for radiation and surgical therapy: a 56% decrease in all 3 parameters in a study with pamidronate [13], and 40% in another one with ibandronate [4]. These data correlate well with our results which show 49% of the patients having complete plus partial response to the bisphosphonate therapy, that is scintigraphically detected decreased to normalized mineral metabolism in the bone lesions. That, together with the number of patients with stable bone lesions (31%), makes 80% of the patients with no disease progression in the skeleton under biphosphonate treatment.

Imaging is a very important part in the management of bone metastases in breast cancer but the best imaging modality (X-ray, WB BSc, computed tomography-CT, MRI, single photon emission computed tomography – SPECT, positron emission tomography – PET) for assessing treatment response has always been questionable because of the consideration of the bone disease as “non-measurable” [7] and because of the advantages and disadvantages that each imaging modality has. According to the practical approach for the evaluation of treatment effect on bone metastases accepted by Hamaoka et al. [7], skeletal scintigraphy should be used to support other imaging modalities for assessing tumor response and is strongly recommended in case of appearance of symptoms of new lesions, worsening of existing ones or biochemical changes indicating progressive disease. Another recommendation was that the modality that gave the most definitive image of bone metastases at diagnosis (WB BSc, X-ray, CT, MRI) should be used again to assess the response of bone metastases to treatment [7]. The use of F-18-PET and the hybrid techniques as SPECT/CT and PET/CT can provide earlier and more accurate detection of osseous metastases providing better treatment response evaluation [8,24], but they are still not widely available and at a much higher cost. So, despite the accepted algorithms, the problem for evaluating the treatment effect on bone metastases remains open.

In our study we used skeletal scintigraphy as a basic imaging modality for monitoring the treatment effect of bisphosphonates in bone metastatic breast cancer and the response we observed correlates well with the worldwide studied effectiveness of bisphosphonates.

In summary, WB BSc is reliable objective functional imaging modality accurately describing the therapeutic effect of biphosphonates on bone lesions of breast cancer and is also a method that can be used in the multimodal treatment planning of breast cancer patients.

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