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Risk of complications from bone metastases in breast cancer: implications for management

T.A. Plunkett *, P. Smith, R.D. Rubens

Academic Oncology Unit, Guy's Hospital, London SE1 9RT, UK

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Abstract

A retrospective analysis of 859 patients who developed bone metastases from breast cancer between 1975 and 1991 was performed in order to identify factors that predict for complications from skeletal disease. The patients were divided into four groups based on the sites of disease at diagnosis of skeletal metastases: bone disease only; bone and soft tissue disease; bone and pleuropulmonary disease; bone and liver disease. Patients with metastatic disease confined to the skeleton were most likely to develop a pathological fracture. The time to long bone fracture was similar for all groups, but the least number of such fractures occurred in patients with bone and liver metastases since their survival was shortest (median: 5.5 months; $P < 0.001$). Patients with bone metastases only were most likely to require radiotherapy to painful osseous deposits ($P = 0.0001$) and most rapidly developed spinal cord compression ($P = 0.01$, data not shown). The results suggest that patients with disease confined to the skeleton at the diagnosis of bone metastases are most likely to develop skeletal-related complications from advanced breast cancer. Such patients may benefit most from treatment with bisphosphonates.

Keywords: Breast cancer; Bone metastases; Radiotherapy; Bisphosphonates

1. Introduction

Post-mortem studies demonstrate that approximately 70% of patients with advanced breast cancer have bone metastases [1]. Bone metastases are a substantial cause of morbidity in these patients. In an earlier study of 498 patients with first relapse in bone from breast cancer, 29% developed one or more of the following complications of metastatic bone destruction: pathological fracture 16%; spinal cord compression 3% and hypercalcaemia 17% [2].

The symptoms from bone metastases predominantly result from osteoclastic bone resorption [3]. Bisphosphonates inhibit osteoclast activity [4] and have been used in the management of patients with bone metastases. Placebo-controlled, randomised trials demonstrated that 3- or 4-weekly administration of intravenous (i.v.) pamidronate reduced the number of skeletal complications (non-vertebral pathological fractures, surgery to bone, hypercalcaemia and radiation to bone) in patients with advanced breast cancer receiving chemotherapy [5,6] and to a lesser extent in patients receiving endocrine therapy [7]. However, in a retrospective analysis, the estimated cost per event saved by pamidronate therapy was $44 600 in patients receiving concurrent chemotherapy and $128 800 in those receiving concurrent endocrine treatment [8].

In order to maximise the cost:benefit ratio for pamidronate therapy, patients most at risk of complications from skeletal metastatic disease need to be identified. We undertook a retrospective analysis of patients with bone metastases from advanced breast cancer in an attempt to identify factors that predict for complications from skeletal disease.

2. Patients and methods

All patients attending the Breast Unit at Guy's Hospital who developed bone metastases between 1975 and 1991 were identified from the database. This database contains information on patient and tumour characteristics, a number of biological features, such as histological

* Corresponding author. Current address: ICRF Breast Cancer Biology Group, Guy's Hospital, London SE1 9RT, UK. Tel.: +44-171-955-2367; Fax: +44-171-955-2026.

E-mail address: plunkett@icrf.icnet.uk (T.A. Plunkett).

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grade and steroid receptor status, details of metastatic involvement, response to treatment and survival. Patients whose only evidence indicative of bone metastases was an abnormal bone scan without any corroborative radiological changes were excluded; the bone scan appearances in such patients were usually consistent with benign changes.

The case notes of each patient were reviewed and the following information was recorded: date of diagnosis of bone metastases; sites of concurrent metastatic disease (soft tissue; pleuro-pulmonary; liver); sites of increased uptake on bone scan at diagnosis of bone metastases (cervical spine; thoracic spine; lumbar spine; sacrum; pelvis; humeri; femora; ribs; sternum; skull; other) and sites with plain radiographic evidence of metastatic bone disease. The following factors related to skeletal complications were recorded: number of fields of radiotherapy at diagnosis and subsequently (treatment for: pain; prophylaxis; cord compression; post-fracture); date and site of pathological fractures; date of spinal cord compression; and date of first episode of hypercalcaemia. The first systemic treatment for advanced breast cancer following the diagnosis of bone metastases was recorded. Standard criteria were used to classify the response to treatment in patients with assessable disease [9].

Clinical management followed consistent guidelines throughout the study period. All patients were assessed clinically on a regular basis, and bone scans, radiographs of regions of increased uptake and chest radiographs were performed in all patients whenever a change in systemic therapy was indicated for recurrent or progressive disease. Routine liver scans were not performed unless there was clinical evidence of hepatomegaly or disordered serum tests of liver biochemistry. Brain scans were only performed for investigation of specific symptoms.

Endocrine therapy has been the initial treatment of choice for symptomatic advanced breast cancer. For premenopausal patients, this has been ovarian ablation (with or without prednisolone) and for postmenopausal women, tamoxifen (with or without prednisolone). The only exceptions to this policy have been those women known to have oestrogen and/or progesterone receptor-negative tumours, women with hormone-resistant disease or patients with life-threatening additional visceral disease, usually affecting the liver. The only major change in treatment policy has been the increased use of adjuvant systemic treatment, principally for patients with axillary node-positive tumours, since the early 1980s. Throughout the study period, radiotherapy has been used as the treatment of choice for palliation of localised bone pain.

Survival curves were calculated using the method of Kaplan and Meier with significance determined using the log rank test. Survival from diagnosis of bone metastases was calculated from the date of diagnosis of bone metastases to the date of death. Patients who were still alive at the time of analysis were censored at the date they were last known to be alive. Time to fracture was calculated from the date of diagnosis of bone metastases to the date of fracture. Patients who were alive without fracture were censored at the date they were last known to be alive. Patients who had died without evidence of fracture were censored at the date of death. The Chi square test with Yates correction was used to determine the difference between categorical variables in 2×2 tables; otherwise the Chi square test was used.

3. Results

1437 patients were identified from the database. Of these, 460 (32%) were diagnosed elsewhere and 111 (8%) were followed-up at other hospitals, so insufficient information was available for inclusion in the analysis. The notes for 7 patients (0.5%) could not be found. Therefore, the records for 859 patients were available for analysis.

The patients were divided into four groups based on the sites of disease at the time bone metastases were diagnosed: patients with bone metastases only ($n=243$, 28%); patients with bone and soft tissue disease only ($n=268$, 31%); patients with bone and pleuro-pulmonary disease, with or without soft tissue disease ($n=237$, 28%) and patients with bone and liver metastases, with or without soft tissue or pleuro-pulmonary disease ($n=111$, 13%). Survival from diagnosis of bone metastases was significantly greater for patients with bone disease only at diagnosis of skeletal metastases ($P<0.001$; Fig. 1). The survival from diagnosis of bone metastases was shortest for patients with concomitant liver metastases (median survival: 5.5 months; Fig. 1). Survival from the diagnosis of bone metastases did not vary during the study period (data not shown).

The time to vertebral fracture was shortest in the bone only group ($P<0.0017$; Fig. 2). There were no differences between the groups in the time to pathological long bone fractures (Fig. 3). However, since patients with bone disease only at diagnosis of skeletal disease lived longest, most fractures occurred in this group (Table 1). 42 of a total of 243 such patients (17%) developed a pathological long bone fracture (i.e. 1 in 5.8 patients), compared with 5 of 111 patients with bone and liver disease (5%) (i.e. 1 in 22.2 patients).

The relationship between long bone fracture and bone scan findings was examined. Patients with bone scan evidence of deposits in the femora or humeri at diagnosis of bone metastases were significantly more likely than other patients to fracture these bones ($P<0.0001$;

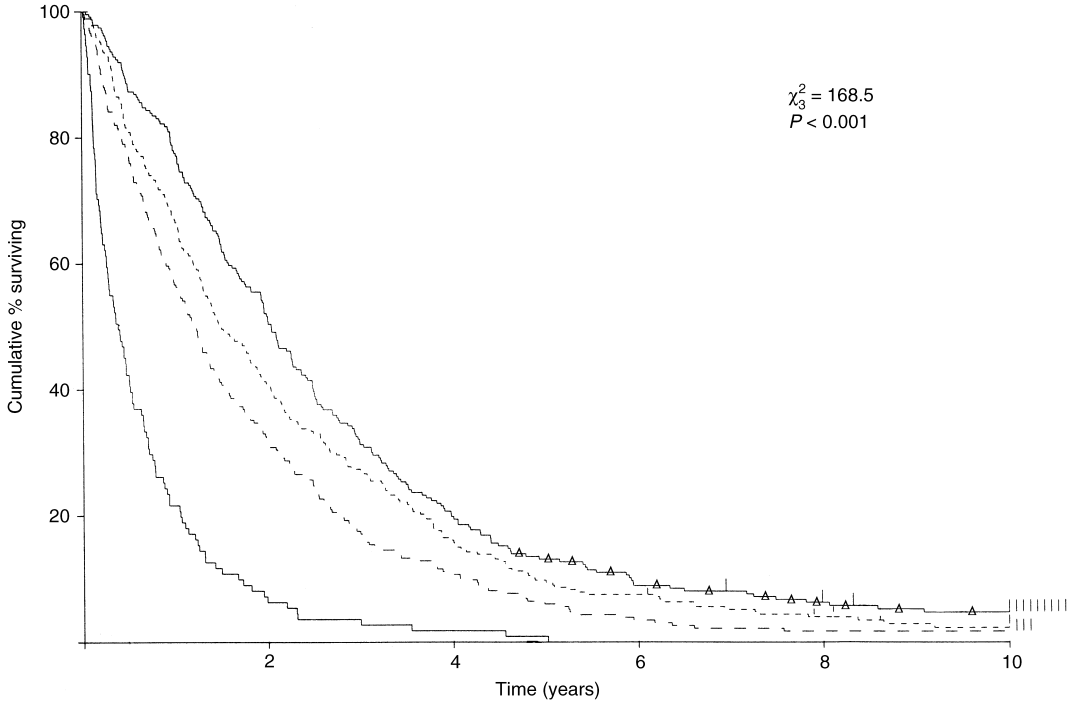

Fig. 1. Survival from diagnosis of bone metastases. –△– Patients with bone disease only at diagnosis. - - - - Patients with bone and soft tissue disease only. – – – Patients with bone and pleuro-pulmonary disease. —— Patients with bone and liver disease.

Table 2). Patients with bone scan evidence of metastases in the femur or humerus were divided according to the presence of osteolytic disease in these bones on plain radiographs. Patients with both scintigraphic and radiographic abnormalities were not at greater risk of long bone fracture ($P = 0.19$, data not shown).

Patients with bone only disease were more likely to have received radiotherapy to bone deposits at diagnosis than patients with additional extra-osseous disease ($P < 0.0001$; Table 3). They were also more likely to receive subsequent radiotherapy ($P < 0.0001$; Table 3). The number of radiotherapy treatments for pain was

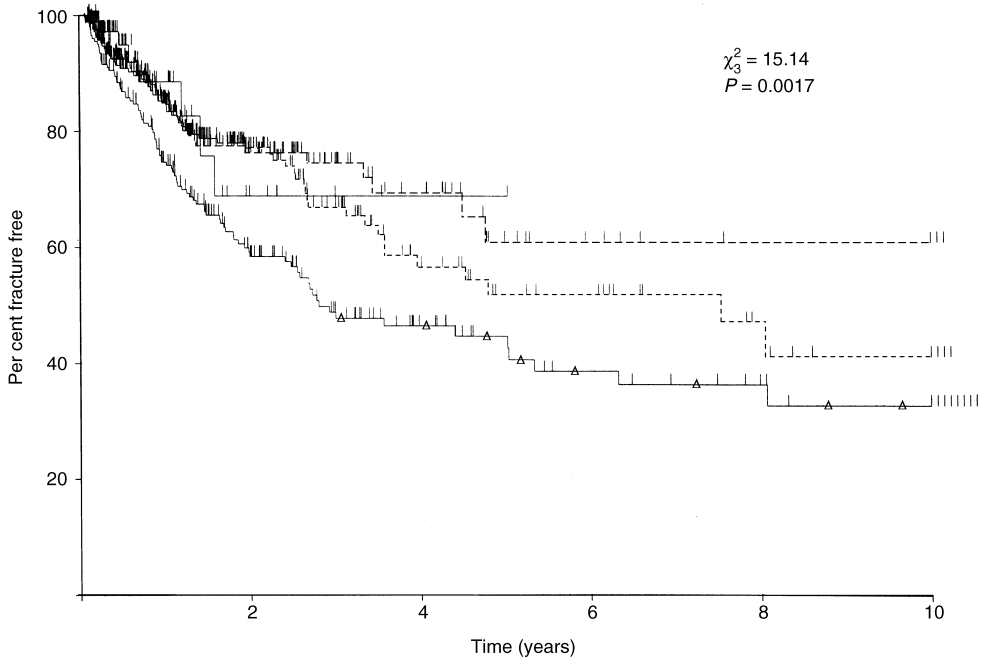

Fig. 2. Time to vertebral fracture. –△– Patients with bone disease only at diagnosis. - - - - Patients with bone and soft tissue disease only. – – – Patients with bone and pleuro-pulmonary disease. —— Patients with bone and liver disease.

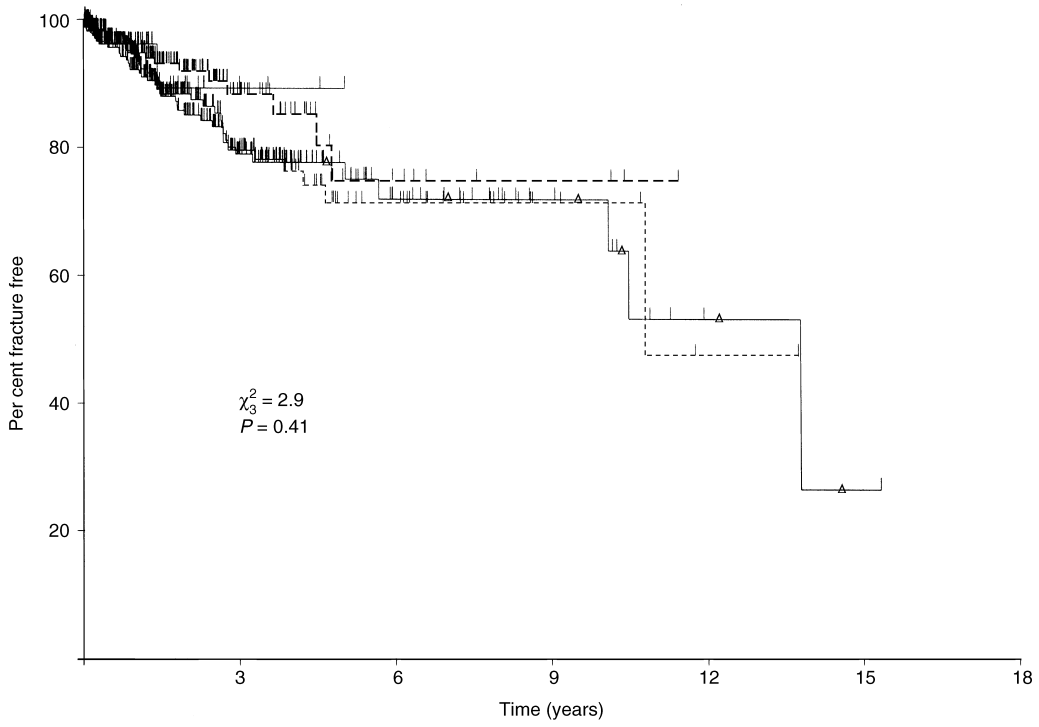

Fig. 3. Time to long bone fracture. –△– Patients with bone only disease at diagnosis. - - - Patients with bone and soft tissue disease only. – – – Patients with bone and pleuro-pulmonary disease. —— Patients with bone and liver disease.

separately analysed. Patients with bone only disease at diagnosis of bone metastases were more likely to receive radiotherapy for painful deposits than patients in the other groups ($P = 0.0001$; Table 4). There were no differences between the groups in the number of radiotherapy treatments for prophylaxis, post-fracture or cord compression.

Patients with bone only disease developed spinal cord compression more rapidly than patients in other groups ($P = 0.01$; data not shown). 36 patients with bone only disease at diagnosis of bone metastases (15%) developed cord compression compared with 2 to 6% of patients in the other groups (Table 1). Bone scan evidence of metastases in the spine did not predict for subsequent development of cord compression (data not shown).

The majority of patients with bone only disease received endocrine therapy as the first systemic treatment following the diagnosis of bone metastases (Table 5); for this group of patients it would have been the first treatment for recurrent disease. Patients in the other groups may have received systemic treatment for recurrent disease at other sites before the diagnosis of bone metastases. Fewer patients in the bone only group achieved a complete or partial response to treatment compared with those in other groups, although the differences were not significant. Response assessment is difficult in osseous disease; when stable disease greater than 6 months was included in the response assessment there were no significant differences between the groups (Table 5).

Table 1
Skeletal complications for all groups of patients

Event	All patients ($n = 859$) n (%)	Bone only ($n = 243$) n (%)	Bone and soft tissue ($n = 268$) n (%)	Bone and pleuro-pulmonary ($n = 237$) n (%)	Bone and liver ($n = 111$) n (%)
Any pathological fracture[a]	296 (35)	128 (53)	91 (34)	55 (23)	22 (20)
Vertebral fractures[a]	173 (20)	79 (33)	47 (18)	31 (13)	16 (14)
Long bone fractures[a]	102 (12)	42 (17)	37 (14)	18 (8)	5 (5)
Fractures at other sites[a]	108 (13)	37 (15)	40 (15)	24 (10)	7 (6)
Hypercalcaemia[a]	162 (19)	62 (26)	44 (16)	30 (13)	26 (23)
Spinal cord compression[a]	64 (8)	36 (15)	15 (6)	11 (5)	2 (2)

[a] Total number of patients that developed complication.

Table 2
Relationship between pathological fracture of the humerus and femur and bone scan findings at diagnosis of bone metastases

	No fracture	Fracture
Humerus		
Bone scan negative	668/687 (97%)	19/687 (3%)
Bone scan positive[a]	138/157 (88%)	19/157 (12%)
	$\chi^2 = 23.78$, $P < 0.0001$	
Femur		
Bone scan negative	541/576 (94%)	35/576 (6%)
Bone scan positive[a]	236/268 (88%)	32/268 (12%)
	$\chi^2 = 7.82$, $P = 0.005$	

[a] Increased uptake within the humerus or femur respectively on bone scan.

4. Discussion

Patients with bone metastases from advanced breast cancer form a heterogeneous group, with many patients having metastatic disease at other sites. For the purposes of this retrospective study, patients were divided on the basis of the sites of disease at first diagnosis of bone metastases.

The results demonstrate that it is possible to define groups of patients with advanced breast cancer at different risks of complications from skeletal disease. Patients with bone only disease at the time of diagnosis of skeletal metastases were 3–4 times more likely to

Table 3
Number of treatments with radiotherapy to the bone according to sites of metastatic disease

	Bone only ($n = 243$) *n* (%)	Bone and soft tissue ($n = 268$) *n* (%)	Bone and pleuro-pulmonary ($n = 237$) *n* (%)	Bone and liver ($n = 111$) *n* (%)
Radiotherapy at time of diagnosis				
No. of fields of treatment				
0	126 (52)	196 (73)	180 (76)	80 (72)
1	85 (35)	51 (19)	36 (15)	20 (18)
$\geqslant 2$	32 (13)	21 (8)	21 (9)	11 (10)
$\chi^2 = 44.32$, df = 6, $P < 0.0001$				
Radiotherapy after diagnosis				
No. of fields of treatment				
0	70 (29)	122 (46)	146 (62)	84 (76)
1	49 (20)	54 (20)	37 (16)	17 (15)
2	44 (18)	29 (11)	26 (11)	4 (4)
3	29 (12)	21 (8)	14 (6)	2 (2)
>3	51 (21)	42 (16)	14 (6)	4 (4)
$\chi^2 = 102.96$, df = 12, $P < 0.0001$				

Table 4
Number of treatments with radiotherapy to bone received by patients for painful metastatic skeletal deposits

No. of fields of treatment	Bone only[a] ($n = 243$) *n* (%)	Bone and soft[b] tissue ($n = 268$) *n* (%)	Bone and pleuro-pulmonary ($n = 237$) *n* (%)	Bone and liver ($n = 111$) *n* (%)
0	41 (17)	64 (24)	110 (47)	68 (61)
1	56 (23)	99 (37)	61 (26)	20 (18)
2	49 (20)	37 (14)	32 (14)	11 (10)
3	34 (14)	21 (8)	14 (6)	9 (8)
$\geqslant 4$	63 (26)	47 (18)	20 (8)	3 (3)
Median (range)	2 (0–12)	1 (0–11)	1 (0–7)	0 (0–8)

[a] $P = 0.0001$ for this group versus the others.

Table 5
Response to first systemic treatment following diagnosis of bone metastases in patients with assessable disease

	Therapy %		Response %	
Disease sites	Endocrine therapy	Chemotherapy	CR + PR	CR + PR + SD
Bone only ($n = 172$)	89	11	19.7	51.7
Bone and soft tissue ($n = 182$)	87	13	26.9	53.2
Bone and pleuro-pulmonary ($n = 174$)	76	24	28.7	52.0
Bone and liver ($n = 72$)	33	66	31.1	43

CR, complete response; PR, partial response; SD, stable disease greater than 6 months duration.

develop pathological long bone fractures than those with bone and liver disease (17% compared with 5%). The time to long bone fracture from diagnosis of bone metastases was similar for all groups, and the overall response rates to treatment were similar. Therefore, the observed difference was most likely attributable to the survival differences between the groups. For example, the median survival from diagnosis of bone metastases for patients with bone only disease was 2.2 years compared with 5.5 months for patients with bone and liver disease.

Scintigraphic evidence of metastases in the femora or humeri at diagnosis correlated with an increased risk of long bone fracture. For example, approximately 1 in 8 patients with bone scan evidence of humeral deposits at diagnosis of skeletal metastases eventually fractured their humerus compared with 1 in 35 patients with no increased tracer uptake in the humerus at diagnosis. However, the presence of identifiable lesions on plain radiographs of the scan abnormality at the time of diagnosis of bone metastases did not specifically identify those at risk of later fracture. It is possible that the use of alternative imaging modalities, such as computed tomography (CT) scanning, may better define those at later risk of fracture. The finding also reflects the long natural history of bone metastases and emphasises the need for continued radiographic monitoring of known sites of disease which are prone to fracture. Specific plain radiographic changes, allied with clinical risk factors, can define groups of patients at high risk of pathological fracture [10].

Vertebral fractures occurred significantly more rapidly in patients with bone only disease compared with patients in the other groups. Women treated for breast cancer have a higher incidence of vertebral fractures than age-matched controls, irrespective of the presence of bone metastases [11]. Chemotherapy and chemotherapy-induced menopause are likely to increase the risk of osteoporosis [12,13], and although tamoxifen may reduce bone loss in post-menopausal women, it may accelerate bone loss in women with normal ovarian function [13,14]. In the present study all women had definite skeletal metastases but it is possible that some vertebral fractures were not a direct result of metastatic disease. Increased resorption and accelerated bone turnover have been demonstrated in biopsies taken at sites distant from skeletal metastases [15]. These effects may be mediated by parathyroid hormone-related peptide (PTHrP). The expression of PTHrP in primary breast cancer has been reported to increase the risk of relapse in bone [16] and experimental studies have demonstrated that PTHrP has a causal role in the pathogenesis of human breast cancer-mediated osteolysis [17]. It is possible that PTHrP expression may, at least in part, explain the apparent predilection for bone of the tumour cells in patients with bone only disease, as well as the increased rate of vertebral fractures in this group of patients.

Patients with bone only disease received significantly more courses of radiotherapy to bone at diagnosis of skeletal metastases than patients in other groups. This is to be expected as patients without extra-osseous disease are likely to have been investigated specifically for symptoms suggestive of bone metastases, whilst in patients with extra-osseous disease, the bone metastases may have been asymptomatic and instead were detected as part of the staging procedure. Patients with bone only disease were, however, more likely to require subsequent radiotherapy. For example, 51% of patients with bone only disease at diagnosis of bone metastases received 2 or more further treatments with radiotherapy compared with 10% of patients with bone and liver metastases.

Patients with bone only disease were more likely to receive radiotherapy for painful skeletal deposits than patients with extra-osseous disease. 83% of patients with bone only disease required radiotherapy for painful skeletal deposits; 60% of these patients required more than one treatment. In contrast, 47% of patients with bone and liver metastases required radiotherapy for relief of pain, and only 21% required more than one treatment. There were no significant differences between the groups in response to first systemic treatment following the diagnosis of bone metastases. The increased need for radiotherapy in patients with bone only disease may instead be a reflection of their prolonged survival compared with the other groups.

The morbidity from bone metastases results mainly from osteoclastic bone resorption [3]. Bisphosphonates inhibit osteoclast activity [4] and have been used in the management of patients with bone metastases. A placebo-controlled trial demonstrated that treatment with pamidronate in patients with bone metastases from breast cancer receiving chemotherapy significantly reduced non-vertebral pathological fractures, surgery to bone, hypercalcaemia and radiation to bone [5,6]. There were quality of life benefits from treatment with pamidronate at 1 year, but no significant differences following 2 years of treatment. A similar study in patients receiving endocrine therapy demonstrated that treatment with pamidronate significantly reduced the need for radiotherapy and hypercalcaemia by 24 months of treatment, but had no effect on non-vertebral fractures and there were no quality of life or performance status benefits [7].

A retrospective cost-effectiveness analysis demonstrated that the cost per event avoided by treatment with pamidronate was $44 600 for patients receiving chemotherapy and $128 800 for patients with hormonal therapy [8]. As hypercalcaemia, should it develop, can be effectively treated with bisphosphonates, the main cost savings from prophylactic therapy are likely to

result from reductions in the rate of non-vertebral fractures and the use of radiotherapy. Non-vertebral fractures include sites such as ribs and long bones. The latter are more costly to the healthcare provider in financial terms and, more importantly, are more costly to the patient in terms of pain and disability. The current study identified groups of patients most at risk of these complications from skeletal metastatic disease. The results might be used to select patients for treatment with bisphosphonates and could improve the cost:benefit analysis. For example, patients with bone and liver disease have the lowest risk of pathological long bone fracture or need for radiotherapy. The median survival for such patients in this study was 5.5 months; pamidronate did not reduce the need for radiotherapy or the occurrence of non-vertebral pathological fractures until approximately 6 and 12 months of treatment respectively [5]. This proposal requires further economic evaluation in a prospective study.

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